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Acromegaly

S. Todorov

Institute of Experimental Morphology and Anthropology with Museum, Bulgarian Academy of Sciences, Sofia

Acromegaly is a hormonal disorder that results from too much growth hormone (GH) in the body. The excess GH comes from noncancerous tumors on the pituitary. The most common symptoms are abnormal growth of the hands and feet, brow and lower jaw protrude, the nasal bone enlarges, and the teeth space out. Surgery is the first option recommended for most people with acromegaly, as it is often a rapid and effective treatment. If the surgery is successful, facial appearance and soft tissue swelling improve within a few days. Medical therapy is most often used if surgery does not result in a cure. From anthropological point of view contemporaries studies on acromegaly are small number. Acromegaly is often difficult to diagnose. Scientists have based their diagnoses almost entirely upon phenotypic characteristics. So further medico-anthropological studies of patients with acromegaly are needed to determine level of abnormal changes.

Key words: acromegaly; pituitary; growth hormone; hypertrophy of the hands, feet and the face.

Introduction

Acromegaly (from Greek 'acros-end' and 'megalos-big') is a hormonal disorder that results from too much growth hormone (GH) in the body. Due to its low frequency and "hidden" onset it is hard to diagnose. In Bulgaria there are 400 registered cases of acromegaly and no full anthropological characterization of specific anomalies (enlargement) that affect the hands and feet as a consequence of the disease.

In 1886 Pierre Marie (1853-1940 Paris, France) used the term "acromegaly" for the first time andgave a full description of the characteristic clinical picture: "A condition characterized by hypertrophy of the hands, feet and the face exists which we propose to be called "acromegaly" which means hypertrophy of the extremities. In reality the extremities are swollen during the disease course and their increase in volume is the most characteristic feature of this disease. Acromegaly is different from myxedema, Paget's disease or leontiasis ossea of Virchow." [8]. Marie, however, was not the first physician to give a clear description of the clinical picture of acromegaly. Others had done this years before him, like (possibly) the Dutch surgeon and active

opponent of superstition and witch-burning, Johannes Wier (1515-1588) already in 1567, or Saucerotte in 1772. Other physicians had also given the disease different names including Alibert in 1822 calling it "Ge'ant scrofuleux", Verga in 1864 calling it "Prosopo-ectasia"and Lombroso in 1869 calling it "Macrosomia". A total of more than 20 physicians had already published ondisorders, which later could be reclassified as cases of acromegaly [11]. In 1886, Marie was not yet aware of any pituitary pathology in patients with acromegaly. In the following years he and his co-workers J. D. Souza-Leite and G. Marinesco significantly contributed to further knowledge on the clinical features and pathology of acromegaly by publishing many important papers in this field: 1. Souza-Leite J. D. (1890) De l'acrome'galie maladie de Marie, Paris; 2. Marie P., Marinesco G. (1891) Sur l'anatomie pathologique de l'acrome'galie.; 3. Marie P (1888) L'acrome'galie.; 4. Marie P. (1888) L'acrome'galie. etc. (see ref. Wouter, W. [13])

Discussion

The pituitary, a small gland in the brain, makes GH. In acromegaly, the pituitary produces excessive amounts of GH. Usually the excess GH comes from benign, or noncancerous, tumors on the pituitary. These benign tumors are called adenomas.

Acromegaly is most often diagnosed in middle-aged adults, although symptoms can appear at any age. If not treated, acromegaly can result in serious illness and premature death. Acromegaly is treatable in most patients, but because of its slow and often "sneaky" onset, it often is not diagnosed early or correctly. The most serious health consequences of acromegaly are type 2 diabetes, high blood pressure, increased risk of cardiovascular disease, and arthritis. Patients with acromegaly are also at increased risk for colon polyps, which may develop into colon cancer if not removed [5].

When GH-producing tumors occur in childhood, the disease that results is called gigantism rather than acromegaly. A child's height is determined by the length of the so-called long bones in the legs. In response to GH, these bones grow in length at the growth plates–areas near either end of the bone. Growth plates fuse after puberty, so the excessive GH production in adults does not result in increased height. However, prolonged exposure to excess GH before the growth plates fuse causes increased growth of the long bones and thus increased height. Pediatricians may become concerned about this possibility if a child's growth rate suddenly and markedly increases beyond what would be predicted by previous growth and how tall the child's parents are.

Hormones never seem to act simply and directly. They usually "cascade" or flow in a series, affecting each other's production or release into the bloodstream.

GH is part of a cascade of hormones that, as the name implies, regulates the physical growth of the body. This cascade begins in a part of the brain called the hypothalamus. The hypothalamus makes hormones that regulate the pituitary. One of the hormones in the GH series, or "axis," is growth hormone-releasing hormone (GHRH), which stimulates the pituitary gland to produce GH.

Secretion of GH by the pituitary into the bloodstream stimulates the liver to produce another hormone called insulin-like growth factor I (IGF-I). IGF-I is what actually causes tissue growth in the body. High levels of IGF-I, in turn, signal the pituitary to reduce GH production [1].

The hypothalamus makes another hormone called somatostatin, which inhibits GH production and release. Normally, GHRH, somatostatin, GH, and IGF-I levels

in the body are tightly regulated by each other and by sleep, exercise, stress, food intake, and blood sugar levels.

In more than 95 percent of people with acromegaly, a benign tumor of the pituitary gland, called an adenoma, produces excess GH. Pituitary tumors are labelled either micro- or macro-adenomas, depending on their size. Most GH-secreting tumors are macro-adenomas, meaning they are larger than 1 centimeter. Depending on their location, these larger tumors may compress surrounding brain structures. For example, a tumor growing upward may affect the optic chiasm–where the optic nerves cross–leading to visual problems and vision loss. If the tumor grows to the side, it may enter an area of the brain called the cavernous sinus where there are many nerves, potentially damaging them [9].

Compression of the surrounding normal pituitary tissue can alter production of other hormones. These hormonal shifts can lead to changes in menstruation and breast discharge in women and erectile dysfunction in men. If the tumor affects the part of the pituitary that controls the thyroid, another hormone-producing gland, then thyroid hormones may decrease. Too little thyroid hormone can cause weight gain, fatigue, and hair and skin changes. If the tumor affects the part of the pituitary that controls the adrenal gland, the hormone cortisol may decrease. Too little cortisol can cause weight loss, dizziness, fatigue, low blood pressure, and nausea.

Some GH-secreting tumors may also secrete too much of other pituitary hormones. For example, they may produce prolactin, the hormone that stimulates the mammary glands to produce milk. Rarely, adenomas may produce thyroid-stimulating hormone. Doctors should assess all pituitary hormones in people with acromegaly.

Rates of GH production and the aggressiveness of the tumor vary greatly among people with adenomas. Some adenomas grow slowly and symptoms of GH excess are often not noticed for many years. Other adenomas grow more rapidly and invade surrounding brain areas or the venous sinuses, which are located near the pituitary gland. Younger patients tend to have more aggressive tumors. Regardless of size, these tumors are always benign.

Most pituitary tumors develop spontaneously and are not genetically inherited. They are the result of a genetic alteration in a single pituitary cell, which leads to increased cell division and tumor formation. This genetic change, or mutation, is not present at birth, but happens later in life. The mutation occurs in a gene that regulates the transmission of chemical signals within pituitary cells. It permanently switches on the signal that tells the cell to divide and secrete GH. The events within the cell that cause disordered pituitary cell growth and GH oversecretion currently are the subject of intensive research [7].

Rarely, acromegaly is caused not by pituitary tumors but by tumors of the pancreas, lungs, and other parts of the brain. These tumors also lead to excess GH, either because they produce GH themselves or, more frequently, because they produce GHRH, the hormone that stimulates the pituitary to make GH. When these non-pituitary tumors are surgically removed, GH levels fall and the symptoms of acromegaly improve [12].

In patients with GHRH-producing, non-pituitary tumors, the pituitary still may be enlarged and may be mistaken for a tumor. Physicians should carefully analyze all "pituitary tumors" removed from patients with acromegaly so they do not overlook the rare possibility that a tumor elsewhere in the body is causing the disorder.

What are the symptoms of acromegaly?

The name acromegaly comes from the Greek words for "extremities" and "enlargement," reflecting one of its most common symptoms–the abnormal growth of the hands and feet. Swelling of the hands and feet is often an early feature, with patients noticing a change in ring or shoe size, particularly shoe width. Gradually, bone changes alter the patient's facial features: The brow and lower jaw protrude, the nasal bone enlarges, and the teeth space out.

Overgrowth of bone and cartilage often leads to arthritis. When tissue thickens, it may trap nerves, causing carpal tunnel syndrome, which results in numbness and weakness of the hands. Body organs, including the heart, may enlarge [14].

Other symptoms of acromegaly include:

- joint aches
- thick, coarse, oily skin
- skin tags
- enlarged lips, nose, and tongue
- deepening of the voice due to enlarged sinuses and vocal cords
- sleep apnea–breaks in breathing during sleep due to obstruction of the airway
- excessive sweating and skin odor
- fatigue and weakness
- headaches
- impaired vision
- abnormalities of the menstrual cycle and sometimes breast discharge in women
- erectile dysfunction in men
- decreased libido

How common is acromegaly?

Small pituitary adenomas are common, affecting about 17 percent of the population. However, research suggests most of these tumors do not cause symptoms and rarely produce excess GH. Scientists estimate that three to four out of every million people develop acromegaly each year and about 60 out of every million people suffer from the disease at any time. Because the clinical diagnosis of acromegaly is often missed, these numbers probably underestimate the frequency of the disease [7].

How is acromegaly diagnosed?

If acromegaly is suspected, a doctor must measure the GH level in a person's blood to determine if it is elevated. However, a single measurement of an elevated blood GH level is not enough to diagnose acromegaly: Because GH is secreted by the pituitary in impulses, or spurts, its concentration in the blood can vary widely from minute to minute. At a given moment, a person with acromegaly may have a normal GH level, whereas a GH level in a healthy person may even be five times higher [1, 6].

More accurate information is obtained when GH is measured under conditions that normally suppress GH secretion. Health care professionals often use the oral glucose tolerance test to diagnose acromegaly because drinking 75 to 100 grams of glucose solution lowers blood GH levels to less than 1 nanogram per milliliter (ng/ml) in healthy people. In people with GH overproduction, this suppression does not occur. The oral glucose tolerance test is a highly reliable method for confirming a diagnosis of acromegaly [3].

Physicians also can measure IGF-I levels, which increase as GH levels go up, in people with suspected acromegaly. Because IGF-I levels are much more stable than GH levels over the course of the day, they are often a more practical and reliable screening measure. Elevated IGF-I levels almost always indicate acromegaly. However, a pregnant woman's IGF-I levels are two to three times higher than normal. In addition, physicians must be aware that IGF-I levels decline with age and may also be abnormally low in people with poorly controlled diabetes or liver or kidney disease [6].

After acromegaly has been diagnosed by measuring GH or IGF-I levels, a magnetic resonance imaging (MRI) scan of the pituitary is used to locate and detect the size of the tumor causing GH overproduction. MRI is the most sensitive imaging technique, but computerized tomography (CT) scans can be used if the patient should not have MRI. For example, people who have pacemakers or other types of implants containing metal should not have an MRI scan because MRI machines contain powerful magnets.

If a head scan fails to detect a pituitary tumor, the physician should look for non-pituitary "ectopic" tumors in the chest, abdomen, or pelvis as the cause of excess GH. The presence of such tumors usually can be diagnosed by measuring GHRH in the blood and by a CT scan of possible tumor sites.

Rarely, a pituitary tumor secreting GH may be too tiny to detect even with a sensitive MRI scan [12].

How is acromegaly treated?

Currently, treatment options include surgical removal of the tumor, medical therapy, and radiation therapy of the pituitary [14].

Goals of treatment are to:

- reduce excess hormone production to normal levels
- relieve the pressure that the growing pituitary tumor may be exerting on the surrounding brain areas
- preserve normal pituitary function or treat hormone deficiencies
- improve the symptoms of acromegaly

Surgery

Surgery is the first option recommended for most people with acromegaly, as it is often a rapid and effective treatment.

Medical Therapy

Medical therapy is most often used if surgery does not result in a cure and sometimes to shrink large tumors before surgery. Three medication groups are used to treat acromegaly.

Somatostatin analogs (SSAs) are the first medication group used to treat acromegaly. They shut off GH production and are effective in lowering GH and IGF-I levels in 50 to 70 percent of patients.

The second medication group is the GH receptor antagonists (GHRAs), which interfere with the action of GH. [3].

Dopamine agonists make up the third medication group. These drugs are not as effective as the other medications at lowering GH or IGF-I levels, and they normalize IGF-I levels in only a minority of patients [3, 10].

Although first researches on acromegaly concern phenotypical onset of the disease and are mainly descriptive (scopic) and includes some basic measurements (metric) so they can be qualified as anthropological studies. From anthropological point of view contemporaries studies on acromegaly are small number. Such a study is published by Dostalova S. et al. [4] and includes 38 patients (12 women and 36 men) passed trough cephalometric examination and 86 persons of control group (36 women and 50 men). The results are showing notables anomalies in patients with acromegaly from both sexes: increased facial high, longer ramus of the mandible and greater distance *basion-supramentale.* In conclusion significant anomalies affecting all orofacial bones except maxilla are found.

Another study concerning body composition of patients with acromegaly regarding quantity of water and fats in the body is presented by Brummer, R. et al. [2]. The design includes 10 patients submitted examination of cellular weight, extra cellular water and fats-free extra cellular solids. The measurement techniques consisted of anthropometry, bioelectrical impedance analysis (BIA)-applying various established regression equations-tritiated water dilution, whole body 40K-counting, and whole body computed tomography. The results are: CT-calibrated anthropometric predictions significantly overestimated body fat. It is concluded that in patients with active acromegaly, the determination of body composition using either certain two-compartment models based on measurement of total body water or bioelectrical impedance, or a four-compartment model based on total body water and total body potassium measurements show good agreement with CT-determined body composition. But this study is mainly comparison of most exact way to determinate the body composition.

Conclusion

Since acromegaly is often difficult to diagnose until later in life, recent studies are focusing on the best and most efficient way to determine a problem before major irreversible damage occurs. Unfortunately, since the disease is so rare, major symptoms generally have to occur before the afflicted is even tested for the disease. The problem is until recently, scientists have based their diagnoses almost entirely upon phenotypic characteristics and what is known about pituitary adenomata. So further medico — anthropological studies on metric and scopic characteristics of patients with acromegaly and comparison with control groups to determine level of abnormal changes occurring orofacial and somatic structures, and may be discover some anthropological signs evoking eventual on set of the disease.

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