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Acromegaly and Gigantism

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1. Introduction

Human growth hormone (GH), a single-chain peptide of 191 amino acids, was isolated from somatotroph cells of the anterior pituitary gland in 1956 and first used therapeutically for treatment of pituitary dwarfism in 1958 (Raben, 1958). Pituitary dwarfism is the classic form of growth hormone deficiency during childhood. Gigantism refers to any standing height more than 2 standard deviations above the mean for the person's sex, age, and Tanner stage. Abnormally high linear growth due to excessive action of insulin-like growth factor-I (IGF-I)/GH causes gigantism while the epiphyseal growth plates are open during childhood, as puberty occurs it is followed by progressive acromegalic changes leading to a picture of a giant with acromegalic features - acromegalic gigantism. When onset disease is after epiphyseal closure, only acromegaly results.

Acromegaly, a somatic growth and proportion disorder first described by Marie in 1886 (Marie, 1886). Elevated levels of growth hormone and IGF-1 are the hallmarks of this syndrome (Melmed, et al., 1983). When Marie first described this syndrome at his patients, pituitary overgrowth is the cause or reflection of the visceromegaly at these patients. In 1909, Harvey Cushing reported the remission of clinical symptoms of acromegaly after partial hypophysectomy, thus indicating the etiology of the disease and its potential treatment as well (Cushing, 1909).

2. Epidemiology

It is a rare condition with a prevalence less than or equal to 70 cases per million and annual incidence of 3 to 4 cases per million (Alexander et al., 1980; Ritchie et al., 1990). Acromegaly occurs with equal frequency in males and females. The mean age at diagnosis is 40-45 years.

3. Pathology, etiology, pathophysiology

GH also called somatotropin is main regulator of normal growth. Its actions responsible for the catching up of normal adult height. The GH gene is located on chromosome 17 (Chen et al., 1989). There are at least three monomeric forms of GH-the predominant physiologic 22 kd form, a less abundant 20 kd form, and a third incompletely characterized form (Lin et al., 1992). The principal GH form in the pituitary is a 191 amino acid, single-chain, 22 kDa protein (22K). It is the product coded for by the GH-N gene (N for normal) and has also

been termed GH-N (Parks, 1989). A second product arising from the same gene is the 20,000 dalton GH variant (20K) (Lewis et al., 1978). This protein is identical to 22K, except for an internal 15 amino acid deletion (residues 32-46). 20K GH is the result of an alternatively spliced GH pre-mRNA where part of exon 3 is spliced out (DeNoto et al., 1981). Importance of this heterogeneity is unknown. Both forms of hormone are secreted and have similar growth promoting activity, although metabolic effects of the 20K form are reduced. 20K has decreased insulin-like and perhaps slightly decreased diabetogenic activity compared to 22K (Baumann et al., 1994).

Once secreted from the pituitary, a substantial proportion of GH circulates bound to GH-binding protein (GHBP) (Baumann et al., 1986; Herington et al., 1986; Leung et al., 1987). There are two forms of GHBP, a low-affinity variety and a high-affinity form. GHBP comprises the extracellular domain of the GH receptor (Leung et al., 1987) which is located in peripheral tissues and mediates the effects of GH on target organs. The GH binding protein and GH receptor are products of the same gene. GHBP is produced by proteolytic cleavage of the receptor at the outer surface of target cells (Harrison et al., 1995). GH binding protein prolongs its half-life and regulates changes in free hormone concentration. Free portion can cross capillary membranes and perform its actions.

GH elicits intracellular signaling through a peripheral receptor and initiates a phosphorylation cascade involving the JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathway (Carter-Su et al., 1996). Liver contains most abundant receptors for GH. When GH receptor activated this causes rapid JAK2 tyrosine kinase activation, leading to phosphorylation of intracellular signaling molecule including the STATs. Phosphorylated STAT proteins are directly translocated to the cell nucleus, where they elicit GH-specific target gene expression by binding to nuclear DNA (Xu et al., 1996).

Growth hormone induces hepatic production of IGF-I responsible of many of its growth-promoting effects. Local production of IGF-I acting either in a paracrine or autocrine manner also has important biological effects, predominant of which is stimulating cell proliferation and inhibiting apoptosis (Le Roith et al., 2001).

Secretion of GH from the pituitary is pulsatile. An average half-life is 10-20 minutes, it is metabolized through the kidneys, liver, or target tissues (Casanueva, 1992). In children and young adults, maximal GH secretion occurs within 1 hour after the onset of deep sleep (stage III or IV) (Finkelstein et al., 1972; Mendelson, 1982; Takahashi et al., 1968). Two hypothalamic hormones regulate GH secretion; Growth hormone releasing hormone (GHRH) provides the primary drive for GH synthesis and secretion by inducing GH gene transcription and hormone release and does not induce other anterior pituitary hormones (Barinaga et al., 1983; Thorner et al., 1984). GHRH is needed for normal pulsatile GH secretion (Painson et al., 1991; Wehrenberg et al., 1982]. SRIF powerfully antagonizes the mitogenic effect of GHRH on somatotrophs, but does not inhibit GH synthesis (Billestrup et al., 1986), suppresses GH secretion mainly by high-affinity binding to SSTR₂ and SSTR₅ receptor subtypes expressed on somatotrophs (Shimon, 1997). It is thought to be interaction between these two hypothalamic hormone plays a role in pulsatile GH secretion.

Ghrelin is another peptide of a primarily gastric origin, although ghrelin mRNA had been found in the hypothalamus playing a role in secretion of GH (Mozid et al., 2003). Synthetic analogues of ghrelin (GHS) had been produced as early as 25 years ago. Acute administration of GHS produces an immediate and massive release of GH. Co-administration of GHS and GH-RH results in powerful GH rise that is greater than the effect

of either peptide administered alone (Bowers et al., 1991). GHS potentiate GH release in response to a maximum stimulating dose of exogenous GHRH (Penalva et al., 1993) and after a saturating dose of GHRH, although subsequent GHRH administration is ineffective, GHS remain fully effective (Jaffe et al., 1993).

Stressful changes in the internal and external environments can produce brief episodes of hormone secretion. Hypoglycemia leads to acute GH secretion, which is the basis for the insulin-induced hypoglycemia test, a gold standard evaluation of pituitary function (Gharib et al., 2003). In man, hyperglycemia causes transient GH suppression for 1 to 3 hours, followed by GH rise 3 to 5 hours after oral glucose administration (Roth et al., 1963). Elevation of free fatty acid levels is a strong inhibitor of GH release in normal humans (Imaki et al., 1985).

Secretory episodes are induced by an increase in certain amino acids, particularly arginine and leucine. Neuropeptides, neurotransmitters, and opiates acts on the hypothalamus by affecting GHRH and SRIF release. Three hours after acute glucocorticoid administration, GH levels rise and remain elevated for 2 hours. Glucocorticoids administered to normal subjects dose-dependently inhibit GHRH-simulated GH secretion, similar to that seen in Cushing's syndrome (Casanueva et al., 1990). While acute glucocorticoid administration stimulates GH secretion, chronic steroid treatment inhibits GH.

Activation of the gonadal system during puberty is accompanied by increased GH and IGF-1 concentrations (Veldhuis et al., 2006; Giordano et al., 2005). Estrogen stimulates GH secretory rates, and testosterone increases GH secretory mass per pulse, with resultant IGF-I induction (Giustina & Veldhuis, 1998).

Chronic malnutrition and prolonged fasting are associated with elevated GH pulse frequency and amplitude (Ho et al., 1988). The maximal GH levels occur within minutes of the onset of slow wave sleep (Holl et al., 1991). Emotional deprivation is associated with suppressed GH secretion and attenuated GH responses to provocative stimuli occur in endogenous depression (Sachar et al., 1972). Exercise and physical stress, including trauma, hypovolemic shock, sepsis increase GH levels (Vigas et al., 1977).

Thyroid disorders also affect GH secretion. Some studies have reported several alterations of the GH/IGF axis and their binding proteins in hypothyroidism. The main alterations reported in untreated adult hypothyroid patients have been low serum concentrations of IGF-1 and IGFBP-3 that increase significantly with restoration of euthyroidism (Miell et al., 1993; Valcavi et al., 1987).

In hypothyroidism, GH pulsatility is decreased and GH responses to a number of secretagogues are attenuated (Valcavi et al., 1992). Fasting serum IGF-1 levels were found significantly lower in the subclinical hypothyroid and with levothyroxine treatment IGF-1 concentrations were significantly increased in subclinical hypothyroid subjects (Akin et al., 2008). Also in hyperthyroidism GH responses to GHRH was found to be decreased whereas serum IGF-1 levels were increased (Valcavi et al., 1993). It could be expected to be decreased due to decreased pituitary GH contents as a result of permanent somatotrophic cell stimulation. At another study, hyperthyroid men is marked by a higher frequency of spontaneous GH secretory bursts, a higher rate of maximal GH secretion attained per burst, and a larger mass of GH released per burst (Iranmanesh et al., 1990). Effects of hyperthyroidism on GH/IGF-1 axis are still controversial. GH-IGF axis was not affected in patients with subclinical hyperthyroidism (Akin et al., 2009).

GHRH have other actions which serve to feed back for GH secretory axis. GHRH stimulates SRIF secretion and inhibits further GHRH secretion in vitro (Aguila et al., 1985). SRIF

inhibits its own secretion *in vitro* (Peterfreund & Vale, 1984). GH and IGF-I feed back to modulate the GH axis at several levels. IGF-I acts directly on the pituitary to inhibit basal and GHRH-induced GH secretion and also to suppress GH gene expression (Berelowitz et al., 1981; Ceda et al., 1987; Ceda et al., 1985, Yamashita & Melmed, 1986; Yamashita et al., 1986). IGF-I also seems to have a direct hypothalamic effect, increasing SRIF secretion (Berelowitz et al., 1981).

A benign somatotroph adenoma of the pituitary is the most common cause of acromegaly. Whether intracellular defects or excessive trophic influences from outside causes pituitary tumor need to be discussed. Growth hormone-releasing hormone has trophic activity in the human pituitary (Thorner et al., 1982) and in addition to a case report of diffuse somatotroph hyperplasia in a patient with a growth hormone-releasing hormone-producing bronchial carcinoid (Ezzat et al., 1994). There are several cases of true somatotroph adenoma formation in patients with growth hormone-releasing hormone-producing hypothalamic gangliocytomas (Asa et al., 1984; Bevan et al., 1989). The clonality of a cellular expansion is a secure archaeological tool capable of distinguishing an irreversible and potentially inexorably progressive process induced by an intracellular insult or insults from a relatively excessive but possibly reversible or self-limiting trophic response to stromal or microenvironmental signals (Levy, 2000; Levy, 2001). The finding of monoclonality in pituitary adenomas is thought to be an evidence for the neoplastic origin of these lesions. Proto-oncogene activation is also a critical prerequisite for pituitary tumor formation.

Pituitary carcinomas are another exceedingly rare cause of acromegaly. Infrequently acromegaly occurs as a result of a hypothalamic tumor secreting GHRH, ectopic secretion of GHRH from a peripheral neuroendocrine tumour (Thorner et al., 1984) or from excessive hypothalamic GHRH secretion (Asa et al., 1984).

Several genetic disorders including multiple endocrine neoplasia type 1 (MEN1) syndrome, McCune Albright syndrome, familial acromegaly and Carney's syndrome are also characterized with growth hormone excess. Postzygotic GNAS mutations result in a mosaic pattern of organ specificity with clinical features of McCune-Albright syndrome (OMIM 174800), including pigmented skin lesions and polyostotic fibrous dysplasia, and endocrine dysfunction including precocious puberty, thyrotoxicosis, and GH and ACTH hypersecretion (Weinstein, 1991).

4. Clinical features of acromegaly

The clinical features of acromegaly are depend on high serum concentrations of both GH and IGF-I (Melmed, 2006). The effect of hypersomatotropism on tissue growth and metabolic function evolves slowly. 10 or more years may elapse from disease onset until diagnosis of the disease (Colao et al., 2004).

Disease can be manifested also with signs and symptoms of pituitary mass. Any pituitary adenoma can cause headaches commonly retro-orbital. Another common symptom caused by the size and location of the tumor is decreased vision. This usually presents as temporal visual field defects. It is caused by the tumor growing upward out of the sella and pressing on the optic chiasm. Other findings include diplopia, ptosis, ophthalmoplegia as a result of extension into the cavernous sinus and compression of the cranial nerves. Sudden loss of vision secondary to apoplexy within the pituitary adenoma may occur. Aggressive tumors can invade the roof of the palate and cause nasopharyngeal obstruction, infection and CSF leakage. Parinaud syndrome is caused by ectopic pinealomas most often accompanied with paralysis of

upward conjugate gaze. As pituitary tumors grow, they compress the pituitary gland, pituitary stalk and hypothalamus and interfere with normal pituitary hormone production. This results in partial or complete anterior pituitary hormone deficiency. Hypothyroidism symptoms, failure to lactate, decreased libido, infertility or oligo/amenorrhoea, sense of not well being are common symptoms of hypopituitarism. Stalk compression leads to hyperprolactinemia. GH-secreting pituitary adenomas may also cosecrete prolactin.

All patients with acromegaly have acral and soft tissue overgrowth, although the extent of the overgrowth varies. Soft tissue findings are macroglossia, large fleshy lips and nose, deepening of the voice, paresthesias of the hands, thickened skin, skin tags, coarsened body hair. Skin tags are common and may be markers for the adenomatous colonic polyps (Leavitt et al., 1983). These soft tissue changes may be attributed to glycosaminoglycan deposition and increased connective tissue collagen production (Verde et al., 1986). Hair growth increases and some women have hirsutism 56 percent in one series (Kaltsas et al., 1999). Acromegalic patients may have a greater incidence of neuropathies because of compression of nerves by adjacent fibrous tissue and endoneural fibrous proliferation. The size and function of sebaceous and sweat glands increase complain of excessive perspiration and body odor. The heart, liver, kidneys, spleen, thyroid, parathyroid glands, and pancreas are larger than normal.

Thyroid dysfunction in acromegaly may be caused by diffuse or nodular toxic or nontoxic goiter or Graves' disease, especially because IGF-I is a major determinant of thyroid cell growth (Kasagi, et al., 1999). As it can be a part of a MEN1 syndrome, hypercalcemia can also be seen.

In the absence of GH there is severe atrophy of the epiphyseal plates, which become narrow as proliferation of cartilage progenitor cells slows markedly.

Conversely, after GH is given to a hypopituitary subject, resumption of cellular proliferation causes columns of chondrocytes to elongate and epiphyseal plates to widen. Synovial tissue and cartilage enlarge, causing hypertrophic arthropathy of the knees, ankles, hips, spine and other joints (Biermasz et al., 2005). Local periarticular fibrous tissue thickening can cause joint stiffening, deformities, and nerve entrapment. Chondrocyte proliferation with increased joint space, ulcerations and fissures of weight-bearing cartilage areas, often accompanied by new bone formation. Chronic osteoarthritis causes narrowed and deformed joint space, osteophyte formation, subchondral cysts, and lax periarticular ligaments with ossification (Dons et al., 1988; 75 Lieberman et al., 1992). When excess GH secretion begins before the epiphyses of the long bones are fused, linear growth does increase; the result is pituitary gigantism. Skeletal overgrowth owing to periosteal new bone formation in response to IGF-1 (McCarthy, et al., 1989). Subtle skeletal and acral overgrowth and soft tissue enlargement causes increased shoe and ring size. Mandibular overgrowth with prognathism, maxillary widening, teeth separation, jaw malocclusion other skeletal manifestations of the acromegaly. Prognathism, thick lips, macroglossia, and hypertrophied nasal structures can obstruct airways (Rosenow et al., 1996; Grunstein et al., 1994). This result in obstructive sleep apnea syndrome. Sleep apnea may also be central in origin and associated with higher GH and IGF-I levels (Grunstein et al., 1994).

Untreated acromegaly results in premature mortality, most commonly from cardiovascular disease (Ritchie et al., 1990; Wright et al., 1970; Etxabe et al., 1993; Rajasoorya et al., 1994; Orme et al., 1998). Asymmetric septal hypertrophy, left ventricular hypertrophy, cardiomegaly and cardiac failure develop; effective treatment reducing growth hormone and IGF-1 serum levels improves cardiac function (Colao et al., 1999). Heart failure occurs in

3 to 10 percent of patients (Damjanovic et al., 2002; Bihan et al., 2004). An increased prevalence of valvular heart disease has also been reported. Arterial blood pressure (systolic and diastolic) is higher with loss of normal daily circadian variability (Terzolo et al., 1999). Hypertension was reported in approximately one third of patients who had acromegaly (Pietrobelli et al., 2001; Minniti et al., 1998). Insulin resistance and diabetes mellitus occur as a result of direct anti-insulin effects of GH (Coculescu et al., 2007; Kasayama et al., 2000).

Several benign and malignant neoplasms, especially in the gastrointestinal tract, have been reported in association with acromegaly (Cheung et al., 1997; Ron et al., 1991), particularly colorectal tubular adenomas and carcinoma (Jenkins et al., 2001; Jenkins, 2006). It is related to disease activity with patients with elevated serum growth hormone and IGF-I levels being particularly prone to developing colonic adenomas (Jenkins et al., 2000). A compelling cause-and-effect relationship of acromegaly with cancer has not been established (Delhougne et al., 1995; Ladas et al., 1994). A recent controlled study in 161 patients revealed no increase in polyp incidence in acromegaly (Renehan et al., 2000). Analysis of nine retrospective reports (1956-1998) encompassing 21,470 person-years at risk, yielded no significant increased cancer incidence (Melmed et al., 2001).

Whether patients with acromegaly are also prone to other malignancies remains controversial. Certainly there is epidemiological evidence in the general population that serum IGF-I levels in the upper part of the normal range are associated with an increased risk of breast and prostate cancer and some reviews have shown the former to be increased in acromegaly (Renehan et al., 2004; Nabarro, 1987).

5. Molecular pathogenesis of acromegaly

GH elicits intracellular signaling through a peripheral receptor and initiates a phosphorylation cascade involving the JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathway (Carter-Su et al., 1996). The STAT proteins become phosphorylated and translocate into the cell nucleus. Transcription of target proteins, such as IGF-I evoke pleiotropic cell responses including IGF1 synthesis, glucose metabolism, cell proliferation, and cytoskeletal changes.

STAT5b is the key intracellular molecule required for GH mediation of postnatal growth, adipose tissue function, and sexual dimorphism of hepatic gene expression (Lanning et al., 2006). In humans, STAT mutations result in relative GH insensitivity and growth retardation (Kofoed, 2003).

6. Diagnosis

Normal GH production from the pituitary gland is pulsatile with the maximal production occurring at night. Even though episodic basal growth hormone secretion patterns are sustained in acromegaly, diurnal variation and the sleep-related growth hormone rise are lost (Barkan et al., 1989). Most values of GH fall in the range of 0.1-0.2 µg/L in normal subjects. However there are six to ten secretory bursts during the day when GH reaches values of 5-30 µg/L, which may overlap with values seen in acromegalic patients. Therefore the only value of a random GH measurement is that of excluding acromegaly if it is undetectable. Unlike the largely undetectable nadir GH levels in normal subjects, those with acromegaly sampled over 24 hours contain detectable levels of GH (>2 µg/L). Elevated integrated growth hormone levels during 24-hour sampling of less than 2.5 µg/L

effectively exclude acromegaly (Duncan et al., 1999). The optimal way to assess the overall daily GH production is to obtain a mean GH over 24 h by frequent GH sampling. However, this method is inconvenient both for the patient and the clinician (Cordero et al., 2008).

The current international consensus for the diagnosis of acromegaly (Giustina et al., 2000) recommends a nadir GH of more than 1 $\mu\text{g/L}$ during an OGTT for diagnosis in conjunction with clinical suspicion and high IGF-1 levels. Using more sensitive newer assays, the GH cut-off may be even lower (Freda et al., 2003). There is a need to verify the current guidelines and propose lowering the current cut off for GH nadir (Costas et al., 2002; Serri et al., 2004). The standard OGTT consists of the administration of 75 g of glucose with GH measurements at various time points for up to 120 min. Normal subjects demonstrate a suppression of GH concentration to 2 $\mu\text{g/L}$ or less throughout the 2 hours of testing (Chapman et al., 1994; Hattori et al., 1990). Acromegalic subjects often gives response paradoxically higher GH levels. Clinicians should be aware that the OGTT's usefulness is limited in high catabolic states, such as stress, hepatic and renal failure, diabetes mellitus, obesity, pregnancy, patients on estrogen replacement or in tall adolescents in whom GH values may be falsely elevated (Duncan et al., 1999; Melmed et al., 2006).

Serum sex and age-matched elevated IGF-1 levels are highly specific for acromegaly in the nonpregnant adult and correlate with clinical disease activity (Clemmons et al., 1979). IGF-1 is an ideal screening test as it has a long half life of 18–20 h and the levels remain stable throughout the day (Giustina et al., 2000). Furthermore IGF-1 correlates with mean GH levels (Barkan et al., 1988) and with clinical features of acromegaly (Clemmons et al., 1979). Even several months after treatment when growth hormone levels are controlled, IGF-1 serum levels may remain persistently high (Drange et al., 1999). Multiple physiologic factors affect IGF-1 levels and need to be taken into account when interpreting the data. IGF-1 is affected by age and gender (Ghigo et al., 1996) with approximately 14% decrease per decade during adult life (Brabant et al., 2003). Again a uniform standard for age range had not been established (Pokrajac et al., 2007) where serum samples with GH and IGF-1 levels close to the current Cortina consensus (Giustina et al., 2000) cutoffs were distributed to different centers to evaluate variability in assay performance. Other problems include the assay susceptibility to interference from binding proteins and the tendency of IGF-1 to plateau at mean GH levels above approximately 20 $\mu\text{g/L}$ (Barkan et al., 1988). The use of exogenous estrogen, malnutrition, liver and renal failure decrease IGF-1 levels (Ho et al., 1922; Freda et al., 2003; Ho et al., 2003). On the other hand, normal pregnancy and adolescence are associated with elevated IGF-1 levels (Duncan et al., 1999).

IGFBP-3 levels are also elevated. However, considerable overlap of these values with those in normal persons, thereby limiting the utility of this measurement.

Magnetic resonance imaging (MRI) of the pituitary gland is the preferred imaging modality for diagnosis in acromegaly. An MRI provides the best assessment of tumor size, location, extent, and relationship to important surrounding structures and is essential for the neurosurgeon to adequately plan surgery and to monitor treatment. If an MRI is not available, a computed tomography (CT) study directed at the pituitary region may be done.

Ectopic GHRH producing tumors may arise from bronchial and pancreatic neuroendocrine tumors, pheochromocytomas, pulmonary endocrine carcinomas, or rarely thymic carcinoid (Vieira et al., 2007; Sugihara et al., 2007; Fainstein et al., 2007; Nasr et al., 2006; Bolanowski et al., 2006; Jansson et al., 1998). The measurement of plasma GHRH concentrations can be very helpful in identifying an ectopic source of GHRH in these particular cases. Total body scintigraphy with radiolabeled somatostatin should be performed to localize the tumor and

to demonstrate somatostatin receptor expression by the tumor which may respond favorably to somatostatin analogue therapy (Kwekkeboom et al., 1993; Drange et al., 1998).

7. Differential diagnosis

Exclusion of an abnormality of the somatotrophic axis in a young patient with acromegaloid features should lead the differential diagnosis towards diagnoses such as pachydermoperiostosis (Hambrick et al., 1996; Rimoin, 1965; Harbison et al., 1971) or insulin mediated pseudoacromegaly, a disorder associated with severe insulin resistance (Flier et al., 1993). These nadir entities must be considered at differential diagnosis of acromegaly.

8. Treatment

Treatment should aim at managing the tumor mass and GH hypersecretion to prevent morbidity and increased mortality while preserving normal pituitary function. Complete surgical removal of GH-secreting tumors results in hormonal control of acromegaly and improvement of soft tissue changes. After successful resection, growth hormone levels return to normal within 1 hour, and metabolic dysfunction and soft-tissue swelling quickly resolve. In patients with intrasellar microadenomas, surgical removal provides biochemical control with normalization of IGF-I in 75–95% of patients (De et al., 2003; Ludecke et al., 2006; Nomikos et al., 2005; Kaltsas et al., 2001; Shimon et al., 2001; Beauregard et al., 2003).

Transsphenoidal microsurgical adenomectomy approach is used most commonly and, in the hands of experienced neurosurgeons, cures the majority of patients who are harboring a well-circumscribed microadenoma and who have serum GH levels less than 40 µg/L (Gittoes et al., 1999; Shimon et al., 2001; Kreutzer et al., 2001). Control rates are lower in patients with noninvasive macroadenomas but even in these cases surgical removal provides biochemical control with normalization of IGF-I in 40–68% of patients (De et al., 2003; Ludecke et al., 2006; Nomikos et al., 2005; Kaltsas et al., 2001; Shimon et al., 2001; Beauregard et al., 2003). The success of surgery depends on the skill and experience of the surgeon in resecting the entire tumor without damaging normal anterior pituitary tissue. Craniotomy is very rarely indicated in patients with acromegaly.

Post-transsphenoidal surgical mortality is rare and most side effects are transient. Permanent diabetes insipidus, cerebrospinal fluid leak, hemorrhage, and meningitis develop in up to 5% and their frequency correlates with tumor size, invasiveness, and neurosurgical experience (Gittoes et al., 1999). In experienced hands, other complications of transsphenoidal surgery are rare including transient oculomotor palsies, deterioration of vision, carotid artery injury and epistaxis (occurring in less than 1% of patients) (Ludecke & Abbe, 2006; Nomikos et al., 2005).

Dopamine agonists (DAs), somatostatin receptor ligands (SRLs), and a GH receptor antagonist (GHRA) are the drug classes available for the treatment of acromegaly. SRLs are the first-choice pharmacotherapy for treating patients who have acromegaly. Two formulas are available for treatment of acromegaly octreotide and lanreotide. Somatotroph and thyrotroph cells express mainly two of five SRIF receptors, SSTR2 and SSTR5 that mediate growth hormone and TSH secretion (Shimon & Melmed, 1998; Weckbecker et al., 2003).

Octreotide is a short-acting somatostatin analogue that binds mainly to SSTR2 and to a lesser extent to SSTR5 (Lamberts, 1988). Lanreotide also acts in a same way. Octreotide also exhibits some SST3 affinity (Patel, 1999). Sandostatin LAR (octreotide acetate) is a long-

acting somatostatin analogue (Flogstad et al., 1995; Lancranjan et al., 1999) requiring monthly injections. Starting dose is 20-mg monthly increasing up to 40 mg depending on clinical and biochemical responses. Depot preparation of lanreotide delivered as an aqueous, small-volume mixture (60, 90, or 120 mg) in prefilled syringes for deep subcutaneous administration every 28 days (Biermasz et al., 2005).

Most studies assessing SRLs efficacy in acromegaly define disease control by mean fasting random serum GH levels less than 2.5 $\mu\text{g/L}$ or normalization of age- and gender-matched IGF-1 plasma levels. Treatment with depot form of lanreotide (60 mg every 21 or 28 days) reduced GH less than 2.5 $\mu\text{g/L}$ in 76% of patients (Attanasio et al., 2003; Ambrosio et al., 2002). In another study, monthly injections sandostatin for 9 years reduced integrated serum GH levels to less than 2 $\mu\text{g/L}$ in more than 75% of patients (Cozzi et al., 2006). More than 70% of patients experience improved general well-being, and soft tissue swelling dissipates within several days of treatment (Ezzat, et al., 1992). Headache, a common symptom in acromegaly, usually resolves within minutes of injection (Pascual et al., 1991) reflecting a specific central analgesic effect.

Joint function and crepitus improve, ultrasound shows evidence of bone or cartilage repair, and after several months, sleep apnea improves (Colao et al., 2004). Asymptomatic patients experience a significant decrease of blood pressure, heart rate, and left ventricular (LV) wall thickness (Colao et al., 2000).

SRLs are effective also in reducing tumor size. Significant tumor size decrease has been reported in 52% of patients on primary therapy (Bevan et al., 2005). A critical analysis of 14 studies reported that 37% of patients treated primarily by SRL experience significant tumor shrinkage (Melmed et al., 2005).

In vivo octreoscan imaging visualizing SRIF receptors demonstrates that GH responsiveness directly correlates with the abundance of pituitary receptors, and patients resistant to octreotide do not have visible receptor binding sites (Ur et al., 1992). Efficacy of octreotide action is determined by frequency of drug administration, total daily dose, tumor size, densely granulated tumors (Bhayana et al., 2005) and pretreatment GH levels.

The use of SRLs is most appropriate; as first-line therapy when there is a low probability of a surgical cure (Melmed et al., 2005; Cozzi et al., 2006; Maiza et al., 2007; Mercado et al., 2007; Colao, et al., 2006) after surgery has failed to achieve biochemical control, before surgery to improve severe comorbidities that prevent or could complicate immediate surgery (Carlsen et al., 2008) to provide disease control, or partial control in the time between administration of radiation therapy and the onset of maximum benefit attained from radiation therapy (Melmed et al., 2009). Gastrointestinal symptoms including nausea, mild malabsorption, flatulence, diarrhea or constipation are common mild side effects of SRLs. Multiple small gallstones and gallbladder sludge may occur, occasionally result in cholecystitis. Abnormal glucose metabolism is described with the use of SRLs, as activation of SST2 and SST5 in the pancreatic insulin-secreting beta cells likely inhibits insulin secretion and counter-regulatory hormones, such as glucagon. Mild hyperglycemia and, rarely hypoglycemia (Bruttomesso et al., 2001) manifest mostly in patients who have pre-existing glucose abnormalities. Octreotide can interact with several drugs including cyclosporine. Absorption of oral hypoglycemic agents, β -blockers, calcium channel blockers can be change and dosage titration should be made slowly with SRL at patients using these agents. Asymptomatic sinus bradycardia can also be seen with these drugs.

Only cabergoline has any efficacy in acromegaly, and this is limited monotherapy effective in less than 10% of patients (Bevan et al., 1992; Colao et al., 1997; Abs et al., 1998; Cozzi et al., 1998). Patients with hyperprolactinemia and minimal GH elevation might benefit most from

dopamine agonist treatment. Main usages of DAs are; when the patient prefers oral medication, after surgery in selected patients, such as those with markedly elevated prolactin and/or modestly elevated GH and IGF-I levels (Melmed et al., 2009) as additive therapy to SRL therapy in patients partially responsive to a maximum SRL dose (Wagenaar et al., 1990; Sadoul et al., 1992; Cremonini et al., 1992; Marzullo et al., 1999; Cozzi et al., 2004; Selvarajah et al., 2005). Side effects of DAs include gastrointestinal discomfort, transient nausea and vomiting, nasal congestion, dizziness, postural hypotension, headache, and mood disorders (Colao et al., 1997). It is known that increased incidence of valvular heart disease with high doses of cabergoline.

GH action through the surface membrane GH receptor is mediated by ligand-induced receptor signaling. The postreceptor GH signal is not elicited if the receptor is bound by pegvisomant, a GH-receptor antagonist, which blocks subsequent IGF-I generation (Trainer, et al., 2000). Daily pegvisomant (20 mg) given for 12 weeks, normalized IGF-1 levels in 82% of patients who had acromegaly (Kopchick et al., 2002). The indications for its use are; in patients that have persistently elevated IGF-I levels despite maximal therapy with other treatment modalities, possibly as monotherapy or in combination with a SRL in other patients (Melmed et al., 2009).

Because elevated hepatic transaminases have been reported (Biering et al., 2006) liver enzymes should be measured every 6 months. Serum GH levels are increased as much as 76% over baseline levels and persistent tumor growth is reported (Trainer et al., 2000) even though, in most cases, GH-secreting adenoma volumes do not change (Van der Lely et al., 2001; Barkan et al., 2005). Current recommendations are to perform a pituitary MRI every 6 months in all patients (Melmed et al., 2006).

Primary or adjuvant radiation of GH-secreting tumors may be achieved by conventional external deep X-ray therapy, proton beam, or gamma knife radiation surgery. It is usually reserved for patients who have postoperative persistent or recurrent tumors that are resistant or intolerant to medical treatment may benefit from radiotherapy. After conventional radiation (up to 5000 rads divided in 180-rad fractions over 6 weeks), tumors cease growing and shrink in most of patients (Biermasz et al., 2000). Conventional radiotherapy (conformal fractionated radiotherapy) can lower GH levels and normalize IGF-I in over 60% of patients, but maximum response is achieved 10–15 yr after radiotherapy is administered (Barrande et al., 2000; Jenkins et al., 2006; Minniti et al., 2005).

Stereotactic radiosurgery using gamma knife delivers a single tumor-focused radiation fraction. Five-year remission rates with gamma knife radiotherapy in patients with acromegaly (after surgical debulking) range from 29 to 60% (Attanasio et al., 2003; Castinetti et al., 2005; Jezkova et al., 2006; Pollock et al., 2007). After 10 years, about half of all patients receiving radiation therapy have signs of pituitary trophic hormone disruption, and this prevalence increases annually thereafter. Side effects of conventional radiation including hair loss, cranial nerve palsies, tumor necrosis with hemorrhage, and loss of vision or pituitary apoplexy (both rare) have been documented in up to 2% of patients (Van der Lely, 1997). Lethargy, impaired memory, brain tumors at irradiation site and personality changes can also occur.

9. Posttreatment follow-up

GH and IGF-I should be measured to assess the biochemical response to any medical treatment. OGTT and IGF-1 measurement with clinical examination should be performed at 3–6 months after surgery, and 3–4 months period thereafter. If patient receives pegvisomant,

monitoring should be made with only IGF-1. OGTT is not helpful in monitoring therapeutic responses while patients are receiving SRL therapy (Arafat et al., 2008; Carmichael et al., 2009). Biochemical control is generally defined as a normal IGF-I for age and gender and age less than 1.0 ng/ml during an OGTT. After biochemical control is achieved, follow up of patients can be made semiannually. With usage of more sensitive GH level less than 0.4 ng/ml thought to be consistent with remission. Pituitary MRI should be performed annually, especially at patients having residual tumor and medical treatment.

Colonoscopy should be performed at three- to four-year intervals in patients over 50 years old and in those with more than three skin tags for early detection and treatment of premalignant colonic polyps (Melmed, 2002). At follow up patients should be evaluated periodically for cardiovascular, skeletal, dental problems.

10. Future prospects of acromegaly

Bogazzi et al. (Bogazzi et al., 2004) reported that thiazolidinedione treatment might slow down the growth of well-established GH-secreting tumors and might effectively reduce the GH hypersecretion. In a study, rosiglitazone, used at maximum approved dosage, did not reduce plasma GH and IGF-1 levels in patients with acromegaly (Bastemir et al., 2007).

In recent years, molecular studies investigated the possible association of gene polymorphisms and susceptibility to diseases. Recently, a polymorphism in the promoter region of the IGF-I gene which is associated with IGF-I serum levels, birthweight and body height in adults has been identified (Vaessen et al., 2001; Rietveld et al., 2004). 194 bp allele (20 CA repeats) of the IGF-I promoter have higher circulating IGF-I levels than others. The patients with 194 bp genotype are the resistant patients with active disease and they required high dose medication responsible from resistance to drugs (Akin et al., 2010). The angiotensinogen MT and AT1R CC1166 genotype carriers may have more risk than other genotypes in the development of hypertension in acromegaly (Turgut, et al., 2011).

11. References

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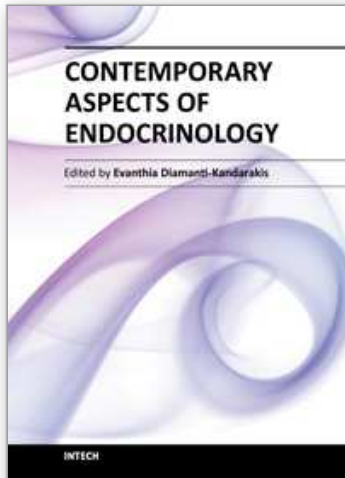
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