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ACROMEGALY

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ABSTRACT

Acromegaly is a hormonal disorder that results from excessive secretion of growth hormone in the body. Commonly affects the adults of middle age group. It is mainly caused by a noncancerous tumor in the pituitary gland. The disease is associated with increased morbidity and premature mortality. It is characterized by progressive somatic disfigurement involving the face and extremities. This in turn would cause various systemic complications. The oral manifestations may be the first to show up the disease in many cases. Hence it is important for oral physicians to be aware of the various changes in the oral and maxillofacial region for early diagnosis and management of the disorder. This article will give an insight about the pathogenesis, clinical features and management of acromegaly.

KEYWORDS: **Acromegaly, Pituitary gland, Endocrine disorder, Stomatostatin.**

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INTRODUCTION

The disease was first identified in a woman in the year 1864 by Verga and was named as "Prosopectasia" then. The term prosopectasia was derived from the greek word "*prosopon"* face and "*ektasis"* stretching[1]. She observed patients with somatic disfigurement, osteoarthropathy, arrhythmias who on postmortem showed giant pituitary in Italy. Brigidi in1881, described acromegaly in Italian actor Ghirlenzoni as he had viseromegaly and enlarged pituitary[2]. They both stated it to be due early menopause or primary bone disease. Massalongo in 1892 and Benda in 1900 stated that the disease have a pituitary origin. Harvey Cushing treated it by partial hypophysectomy and as it showed regression of symptoms it was considered the potential mode of treatment[3]. The symptoms are charecterised by extensive disfigurement with numerous systemic complications. The diagnosis can be made with the clinical features itself. It may include goiter, reproductive disorder, cardiovascular disorder, carpel tunnel syndrome etc[3].

ETIOLOGY[4,5]

Acromegaly can be caused due to pituitary and extra-pituitary disorders. Pituitary causes are somatotrope pituitary adenoma, growth hormone secreting carcinomas, silent somatotrope adenoma, genetic syndrome like fibrous dysplasia can be associated with acromegaly. The adenoma can also be a part of familial multiple endocrine neoplasia(MENS-1) syndrome. Extra pituitary causes can be gangliocytoma, hamartoma, choristoma.

PATHOGENESIS

Acromegaly is a debilitating acquired disorder that usually occurs due to excess production of growth hormone[6]. Since the disease shows a very slow progress, diagnosis is usually delayed by 4 to more than 10 years after its onset[7]. Disease pathogenesis involves GH hypersecretion by tumours pituitary somatotroph cells. Hypothalamic and pancreatic GH and somatostatin as well as growth factors, facilitate the expansion of the population of somatotrophstumour cells. Thus a broad spectrum of changes in growth factor levels can induce a cascade of genetic events, ultimately leading to pituitary cell transformation and the genesis of adenomas[8]. It is mediated by elevated levels of insulin like growth factor1-IGF-1, which is produced in the liver in response to GH[9,10]. Along with changes due to GH and IGF-1 levels, the tumour mass itself may induce optic nerve, chiasma, or tract compression, cranial nerve palsies, head ache, hydrocephalus, and hupopitutarism[11.] The anabolic effects of GH are mediated by insulin like growth factors (IGF-1) and include increase in body size, enlargement of abdomen and head,weight gain, organomegaly of heart, kidney,liver and tongue. Increased production of GHRH from central and peripheral hypothalamic sources can lead to somatotroph hyperplasia and acromegaly[12]. Acromegaly would lead major systemic problems like diabetes, high blood pressure, increased risk of cardiovascular diseases and arthritis[13]. The clinical impact of acromegaly can be determined by echocardiography and sleep apnea[14].

CLINICAL FEATURES [7,13,14]

Acromegaly shows a wide range of clinical signs and symptoms. It involves almost all the system of the body (Table 1).

SKIN CHANGES[12]

Skin is thickened due to glycosaminoglcans deposition and increased collagen synthesis. Skin tags indicative of colonic tags are seen. Raynauds disease can be seen.

BONY CHANGES[12]

Craniofacial changes[15]

Growth hormone and Insulin growth factor 1 causes increased periosteal new bone formation leading to skeletal bone growth which manifests as mandibular prognathism, thickening of the jaw bone, spacing in teeth, malocclusion, macroglossia, frontal bossing, nasal bone hypertrophy. Radiograph shows thickening of

cranial vault, frontal internal hyperostosis, thickening of sellatursica, hypertrophy of frontal sinuses and hypertrophy of larynx causing hoarseness of voice.

Extremities[12]

Excess secretion of growth hormone causes excess growth of hormone and cartilage resulting in bone formation thereby leading to diaphysis in cortical bone, widening of joint spaces.

Trunk[11,12]

The spine undergoes upper dorsal kyphosis and lumbar hyperlordosis.Vertebral enlargement, widening of vertebral spaces and osteophytes. Protruberance of lower portion of sternum, elongation and divergence of ribs.

Limbs[11,12]

Radiograph shows cortical thickening of long bones and widened joint spaces.

Table 1
Clinical manifestations of acromegaly [14,15,16]

SYSTEM INVOLVED	MANIFESTATIONS
Effect of the tumor	Head ache, Visual disturbances.
Skin changes	Increase in thickness of the skin, Hyperhidrosis, Skin tags.
Soft tissue changes	Visceromegaly, Macroglossia.
Bone and Joint changes	Increased articular thickness, Arthralgia, Arthritis, Carpel Tunnel Syndrome, Malocclusion.
Cardiovascular features	Cardiomyopathy, Congestive cardiac disease, Arrhythmias, Hypertension, Ventricular hypertrophy.
Respiratory manifestations	Airway obstruction due to macroglossia, Sleep apnea, Ventilatory dysfunction.
Endocrine disorders	Goiter, Thyrotoxicosis, Hyperparathyroidism, Menstrual abnormality, Gonadal dysfunction.
Metabolic disorders	Impaired glucose tolerance, Diabetes mellitus, Increased nitrogen retension, Hypercalciuria, Reduced total cholesterol and Increased triglycerides.

COMPLICATIONS DUE TO ACROMEGALY [11,12,15,16]

Rheumatologic complications: Arthralgia is due to mechanical, degenerative and non-inflammatory cause. Features resemble osteoarthritis. Shoulders and hip shows loos of mobility.Overgrowth of bone and cartilage leading to arthritis. When tissue thickens it causes joint swelling, pain.

Neuropathy

Carpel tunnel syndrome resulting in numbness and weakness of hands is seen[8].This is due to the compression of nerve due to thickening of nerve. Visual impairment can be seen due to optic nerve compression.

Cardivascular Manifestation

Arterial hypertension due to chronic hypervolemia, endothelial dysfunction and partly due to insulin resistance and diabetes occurs. Acromegaly in absence of other contributing factors is the acromegalic cardiomyopathy[17]. Females are more commonly affected. There can also be cardiac hypertrophy, arrythymias, coronary diseases. Risk of valvular disease and ventricular hypertrophy is also high.

Respiratory manifestations

Impairs respiratory function is seen. Obstructive sleep apnea are common in men who snore and is common in fatigue, weakness, and headache. This brings changes in facial skeleton, jaw opening, and increased laryngeal soft tissues[12].

Endocrine complication

Growth hormone in excess leads to insulin resistance in the liver, impaired glucose tolerance develops followed by diabetes. It decreases the fat mass and increases lean body mass[12].Other features includes menstrual abnormality in females ,erectile dysfunction in males., impaired vision, galactorrhea, goitre, and hypercalcinuria..

Gastrointestinal manifestation

Patients with acromegaly have a larger colon. They have an increased risk of colon polyps which when not removed leads to colon cancer [11,12,15].

DIAGNOSIS

Biochemical analysis

Oral glucose tolerance is considered the gold standard for acromegaly, the inability to suppress serum GH to less than 1ng/ml after administration of 75mg of glucose is consistent with diagnosis[14]. IGF -1 is an integrated marker of GH secretion an elevated level of IGF_1 compared with age and sex normative data range is supportive in diagnosis[18,19].

Imaging

Magnetic resonance imaging(MRI)

It is the most sensitive and best imaging technique to pinpoint pituitary source of excess GH.MRIis neuroradiological examination of choice for all the patients with pitutary adenomas. It gives details of tumour size, volume and invasiveness. Ectopic tumors as a cause of excess GH is diagnosed by measuring GHRH in blood or CTscan of possible tumor site[16].

Others includes visual field testing if tumour compresses optic chiasma, chest x -ray, ECG etc[18,19.]

MANAGEMENT[18]

Goals of management:

- Normalize disease marker (IGF-1, GH)
- Slow or reverse clinical signs and symptoms
- Preserve normal pituitary function
- Restore life expectancy.

The management depends upon patients age, general health, the severity and complications of the disease, and the risk of a particular treatment modality. The major modalities of managementincludes medical, surgical and radiation therapy.

SURGICAL THERAPY

The first line of therapy for acromegalic patients should be transsphenoidal surgery Cure rates reflects the surgical procedures conducted by the surgeon. Follow up should include MRI 1 year after surgery and serial GH and IGF-1 levels and glucose tolerance test. It is a rapid and effective treatment. Most successful in patients when GH concentrations are low less than 10 ng/l or 30 MIU/l[12,18,19].

MEDICAL THERAPY

Medical therapy is an adjuvant to surgical therapy. The three main groups of drugs used somatostatin analog, dopamine agonist, GH receptor antagonist.

Somatostatin analogs[3,15,16,18,19]

The bind to somatostatin receptorson somatotroph adenoma to suppress GH release. Octreotide decreases GH hypersensitivity in acromegaly patients in 30-60 minutes of injection. Its long acting hence given as monthly intramuscular injections Lanreotide is given subcutaneously. These drugs are less effective in large tumours. The side effects includes assymptomatic cholesterol gall stone development, loose stools, nausea, flatulence, hair loss, bradycardia,hyperglycemia.

Dopamine agonists[16,18,19]

They include bromocriptine, pergolide. They lower GH and IGF-1 levels but their therapeutic role is limited. Hence they can be an adjunct along with other therapy. Bromocriptine20mg/ day orally every 6 hours for an optimum treatment efficacy.The advantages are it is available in oral formulation and low cost. Side effects includes nausea,headache, light headed ness,, nasal stuffiness, sleep disturbances,and arrythymias.

Growth hormone receptor antagonist[18]

Pegvisomant, a newer drug is a synthetic GH molecule whichbind to Growth hormone receptor causing functional blockade of GH-mediated intracellular signaling thereby reducing circulating IGF-1.

RADIATION THERAPY[12,18]

Indicated for patients whom the conventional therapy fails and for those with remanant tumour after surgery. On an average 50GY of total dose is delivered in conventional fractionated daily doses. It includes both conventional and stereotactic, stereotactic allows a precise target of high dose beam of radiation at the tumour

from varying angles it is considered to be an effective method of dose delivery.

CONCLUSION

Acromegaly is an uncommon disease.,due to a pituitary tumour. Usually diagnosed by GH and IGF-1 after an oral glucose tolerance test. Since it is a slowly progressive disease there might be a delay in diagnosis. Hence It is essential to be aware of the manifestations for early identification of the disorder and prompt treatment. As the disease involves all the system of the body periodic monitoring of all the systems is essential to improve life expectancy. The recent formulations of octreotide will reduce the role of surgery in future. Though the treatment options include medical, surgical and radiation therapy, the appropriate use of treatment options will ensure an optimal care ofacromegalic patients and will significantly decrease the mortality and morbidity associated with this disorder.

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