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Lect.4

ACROMEGALY

Growth hormone (GH) stimulates the production of insulin-like growth factor 1 (IGF-1), which is produced in the liver and many other tissues. IGF-1 is the main tissue mediator of the actions of GH.

Acromegaly and gigantism are rare disorders caused by excessive secretion of GH, or rarely ectopic production of GH or GH-releasing hormone (GHRH). Acromegaly causes an overgrowth of all organ systems, bones, joints and soft tissues.

Gigantism occurs when an excess GH or IGF-1 occurs before the end of puberty and epiphyseal closure, leading to increased linear growth.

Aetiology

Acromegaly is usually caused by a pituitary tumour (1:3 microadenoma to macroadenoma).

Rarely, ectopic GH from non-endocrine tumours - eg, lung cancer, cancer of the pancreas or ovarian cancer - leads to acromegaly. In very rare cases, excess GHRH arises from a hypothalamic tumour or from a neuroendocrine tumour of the lung or pancreas.

Due to the insidious onset and slow progression, diagnosis is often delayed, particularly in adults, by on average 4-7 years or longer, after the onset of excessive GH secretion[1].

There are several familial causes, including those associated with other endocrine disorders (multiple endocrine neoplasia type 1, McCune-Albright syndrome and Carney complex) or as an isolated disorder, called familial isolated pituitary adenoma (FIPA)]:

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Presentation]

Often an insidious onset and symptoms may precede the diagnosis by several years.

Due to tumour:

Headaches (55%).

Visual field defects: the most common defect is a bitemporal hemianopia.

Due to excess of GH:

Gradual change in appearance due to the effects on cartilage and soft tissues: enlargement of hands and feet (increase in ring and shoe size), frontal bossing, thickening of the nose, enlarged tongue (macroglossia), growth of the jaw (prognathism) and coarsening of facial features.

Macroglossia may cause obstructive sleep apnoea leading to daytime tiredness.

Dental changes: separation and jaw malocclusion.

Excessive sweating (65%) and thick, oily skin, with development of skin tags. Women may have mild hirsutism.

Articular overgrowth of synovial tissue and arthropathy leading to arthralgia and osteoarthritis in 24%, back pain and kyphosis.

Visceral hypertrophy - eg, heart, thyroid (with a multinodular goitre), liver and spleen.

Nerve compression symptoms may occur, especially carpal tunnel syndrome (20-40%).

Cardiac features include hypertension (40%), left ventricular hypertrophy, cardiomyopathy and arrhythmias.

Type 2 diabetes mellitus (40-52%) and glucose intolerance (28-46%) due to insulin resistance.

Colonic polyps.

Vertebral fractures, possibly due to low-quality bone despite high bone mass.

Due to associated hyperprolactinaemia - eg, galactorrhoea, amenorrhoea: in one third of patients with a GH-producing adenoma, the adenoma is also prolactin-secreting[].

Hypopituitarism: decreased secretion of anterior pituitary hormones and compression of pituitary stalk

*Investigations]*

IGF-1 is recommended as the initial screen for suspected acromegaly:

It has a correlation with GH levels, long half life of 15 hours and relatively stable serum levels.

Highly sensitive, such that a normal level usually excludes acromegaly.

False positives may occur in pregnancy and late adolescence.

Hepatic disease and chronic kidney disease, malnutrition, hypothyroidism, severe infection and poorly controlled diabetes may affect IGF-1 levels.

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Oral glucose tolerance test is used to confirm a raised IGF-1:

GH is normally inhibited by glucose. If the glucose load fails to suppress the GH level below 1.0 mcg/L this confirms the diagnosis of acromegaly.

**Random GH is not recommended; secretion is episodic and the half-life is short**.

GHRH concentration can be obtained if clinically indicated.

Assessment of other pituitary hormones as clinically indicated: prolactin, adrenal, thyroid and gonadal hormones.

MRI scan of pituitary and hypothalamus: more sensitive than CT scan.

Visual field tests are used:

If a tumour is found to abut the optic chiasm on imaging.

In pregnant women with a macroadenoma, when they may be performed serially.

CT scan may be indicated: for lung, pancreatic, adrenal or ovarian tumours that may secrete ectopic GH or GHRH.

Total body scintigraphy with radio-labelled OctreoScan® (somatostatin) may be used to aid localisation of the tumour but is rarely required.

Cardiac assessment: electrocardiogram, echocardiogram.

Screening for cancer]

Patients with acromegaly have an increased risk of colon cancer and thyroid cancer. The prevalence of breast and prostate cancer is not increased.

Thyroid cancer is the most common cancer associated with acromegaly[4]:

A thyroid ultrasound is recommended if there is palpable thyroid nodularity, which occurs in over half of patients.

Incidence of thyroid cancer is 1.2-7.2%.

It is not known if the increase in thyroid cancer is a specific effect of GH/IGF-1 or a result of the increased use of more precise diagnostic techniques].

Because of the increased prevalence of colorectal adenomas and cancer, it is recommended that patients with acromegaly should be offered regular colonoscopy screening, starting at the age of 40 years, although screening at diagnosis has also been suggested regardless of age (however, this is controversial). The frequency of repeat colonoscopy should depend on the findings at the original screening and the activity of the underlying acromegaly:

Patients with an adenoma at first screening or persistently elevated serum IGF-1 level above the maximum of the age-corrected normal range should be offered 3- to 5-yearly screening.

Patients with a negative first colonoscopy or a hyperplastic polyp or normal GH/IGF-1 levels should be offered screening every 5-10 years.

Differential diagnosis

Pseudo-acromegaly is the presence of a similar physical appearance in the absence of elevated GH or IGF-1. Causes of pseudo-acromegaly include insulin resistance associated with hyperinsulinaemia and minoxidil treatment].

Management]

The aim of management is to control the symptoms caused by the local effects of the tumour and those due to the excess hormone production, and to normalise hormone levels. No single treatment is completely effective in achieving these aims and so a combination of treatments is required.

Trans-sphenoidal surgery is the treatment of choice in most cases:

Endoscopic trans-sphenoidal treatment for GH-secreting pituitary adenomas has shown similar outcomes for non-invasive macroadenomas compared with traditional microsurgical techniques[8].

Technique chosen depends on the expertise and preference of the surgical team and on patient choice.

Best reported surgical rates for microadenomas and macroadenomas are 81-100% and 45-68% respectively.

Patients with residual disease are offered adjuvant drug treatment to reduce GH levels.

Radiotherapy is used for refractory disease, as an adjuvant for large invasive tumours and when surgery is contra-indicated. The mortality rate is higher in patients treated with radiotherapy].

Genetic counselling is important in young people presenting with acromegaly or gigantism, regardless of family history, as many genetic causes have reduced penetrance and first-degree relatives may not be affected[9].

Drug treatment]

Somatostatin analogues (somatostatin receptor ligands) are the first-choice medical treatments:

Octreotide and lanreotide are analogues of the hypothalamic release-inhibiting hormone, somatostatin.

Maximal benefit may be achieved after more than 10 years of treatment.

Side-effects are frequent and include abdominal discomfort and gallstones or gallbladder sludge; ultrasound is advised if the patient develops symptoms suggestive of gallbladder disease].

Dopamine agonists:

Bromocriptine, cabergoline and quinagolide are effective but are less effective than somatostatin analogues].

Cabergoline is the most effective dopamine agonist, is well tolerated and is safe to use in pregnancy. Cabergoline is suggested in a patient with only modestly raised IGF-1 and mild symptoms and signs of GH excess].

Chronic use of ergot-derived dopamine agonists is associated with a risk of fibrosis, particularly cardiac fibrosis. Cardiac valvulopathy should be excluded by echocardiography before treatment with cabergoline or bromocriptine. Patients commenced on cabergoline should be monitored for signs of cardiac fibrosis during treatment, including echocardiography within 3-6 months of starting treatment and subsequently at 6- to 12-monthly intervals. Treatment should be stopped if echocardiography shows new or worsened valvular regurgitation, valvular restriction or valve leaflet thickening].

The commonly held view that tumours that also secrete prolactin have a better response rate to dopamine agonists is not supported.

Pegvisomant (PEG):

This is a genetically modified analogue of human GH and a highly selective GH receptor antagonist which blocks the peripheral synthesis of IGF-1.

It has been shown to normalise IGF-1 levels in 68-87% of patients: stringent upward dose titration appears to be needed to achieve the best results.

In contrast to somatostatin analogues, PEG decreases fasting glucose and improves glucose tolerance.

GH levels increase during treatment so cannot be used for monitoring. No decrease in tumour size is seen and rarely the pituitary tumour may grow (2.2% of cases) - serial MRI imaging is suggested.

PEG is well tolerated but is associated with raised liver enzymes. Monthly LFTs for the first six months and then every six months is advised

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Pregnancy]:

Medical therapy is withheld during pregnancy.

Short-acting octreotide may be used as needed when attempting to conceive.

Patients with macroadenomas should be monitored for headaches and visual symptoms and undergo serial visual filed testing.

In reports of almost 80 women with prolactinomas, cabergoline has been shown to be safe to the fetus.

Pregnancy in women with active or uncontrolled acromegaly may be associated with an increased risk of gestational diabetes and gravid hypertension].

Complications

Hypertension, coronary heart disease, cardiac failure, cerebrovascular disease.

Diabetes.

Acromegalic arthropathy, which affects up to 70% of patients and involves both the axial and peripheral skeleton.

Obstructive sleep apnoea.

Increased incidence of colonic polyps and adenocarcinoma of the colon.

Increased incidence of nodular goitre and thyroid cancer.

Patients may develop hypopituitarism immediately after surgery, or several years after radiotherapy.

Damage caused by the tumour may result in hyperprolactinaemia and deficiencies of glucocorticoids, sex steroids and thyroid hormone.

Psychological changes, including impaired self-esteem and social withdrawal, as well as anxiety and depression may be problematic in some. An impaired quality of life is common...