

Critically evaluate the role of the Clinical Chemistry laboratory in the investigation, diagnosis and monitoring of a patient thought to have acromegaly

General Comment

This was a very specific question about the laboratory's role in the diagnosis, investigation and management of a patient suspected to have acromegaly.

It was, rather disappointingly, very poorly answered. Most candidates discussed in detail a) the clinical manifestations of acromegaly which were largely irrelevant b) physiology of the hypothalamic-pituitary- target organ axes with little context to Clinical Biochemistry.

Only one candidate mentioned a current important topic – standardisation of GH assays and reporting units.

Many candidates gave factually incorrect information and this was very disconcerting when discussing interpretation of clinical biochemistry tests.

Answer:

Introduction:

- Acromegaly is a rare with an incidence of 3-4 new cases per million of population.
- Acromegaly is the result of dysregulated growth hormone hypersecretion.
- Important to diagnose because of increased mortality (x2) from cardiovascular disease and diabetes.
- Most are due to pituitary GH secreting adenoma.
- Very rarely is the result of ectopic secretion of growth hormone releasing hormone (GHRH) from a peripheral neuroendocrine tumour, or from excessive hypothalamic GHRH secretion.
- 5% of cases are associated with familial syndromes, most commonly multiple endocrine neoplasia type 1 (MEN1) syndrome, but also McCune Albright syndrome, familial acromegaly and Carney's syndrome

- Clinical Biochemistry has a role in the diagnosis, investigation and monitoring of acromegaly
- It is essential to obtain a biochemical diagnosis of acromegaly before undertaking other radiological, optometric investigations

Diagnosis of acromegaly:

- Index of clinical suspicion – mainly physical appearance
- Rarely family screening or in the investigation of MEN type1

- Limitations of random GH. A random GH of <0.4 ug/l (and normal IGF-1) effectively excludes acromegaly

- Raised random IGF-1 may be of value eg in insulin dependent diabetes when it may not be possible to undertake an OGTT. IGF-1 concentrations dependent on normal liver function, renal function, nutritional status

- Gold Standard: 75G OGTT with ½ hrly GH measurement for 120 (-150) mins.

- OGTT requirements: A diet containing at least 150g carbohydrate daily and usual activity for at least 3 days prior to the test. Fast for 12 hours, drink water only. No smoking permitted on the morning of the test or during the test. Volume of glucose solution 250-300mls. Restrict physical activity during test
- Interpretation:
 - Normal response GH suppresses to <0.2 ug/L
 - Acromegaly: Failure of GH to suppress to <1ug/L
 - Acromegaly: Paradoxical increase in GH
 - 25% of acromegalics have IGT/DM on OGTT
- False positives: diabetes mellitus, liver disease, renal disease, adolescence (and anorexia nervosa) – NB IGF-1 discriminator
- Others diagnostic tests:
- GH response to TRH: GH measured at 0, 20, 60 minutes
 - 200ug IV TRH after basal sample
 - Normal subjects GH falls
 - Acromegaly (60%) paradoxical increase in GH
- 24h GH profile:
 - Normal peaks and troughs mean GH <2.5ug/L
 - Acromegaly: loss of pulsatility and mean GH >2.5ug/L
 - Rarely used but correlates well with OGTT

Further biochemical Investigation in proven acromegaly

Local effects of tumour:

Biochemical investigations for hypopituitarism:

Anterior pituitary function stimulation tests

- IST/TRH/LHRH
 - Contra-indications: Ischaemic heart disease, Epilepsy or unexplained blackouts, 09.00h serum cortisol <100nmol/L
 - Medical supervision mandatory – dangerous test
 - Brief summary of protocol and interpretation
- Synacthen/TRH/LHRH
 - Acceptable alternative to above
 - Brief summary of protocol and interpretation
- Minimum: Synacthen test and basal LH, FSH, Testosterone or oestradiol; Prolactin; Free T4 and TSH

Very rarely, if indicated, posterior pituitary function

- If indicated: Paired serum urine osmolalities
Water deprivation test.

Biochemical investigations for systemic effects of excess GH:

Investigation for associated familial syndromes especially MEN type 1 (serum calcium)

PCOS

CVD: Lipids

Immediate Post-operative:

Anterior and posterior pituitary function as above

Limitations of synacthen test

Long-term/medical treatment:

Cure/Monitoring: OGTT

IGF-1

Random GH: varying cut-offs

Cure: Nadir GH during OGGT of <1ug/L and normal IGF-1

Anterior (Posterior) Pituitary function: as above

Assays:

Specific problems with GH assays and standardisation

Discrepancies between GH assays:

- Heterogenicity of GH
- Calibrants with different characteristics,
- Different units (mU/l and µg/l),
- Variety of unit conversion factors,
- Variability in antibody specificity
- International Standard (IS) for GH (WHO IS 98/574) - recombinant material consisting of 22 kD GH of > 95% purity - ; single traceable calibrant for GH immunoassays. To standardise GH measurement, it is recommended that the reporting of GH concentrations in µg/l of IS 98/574 (1 mg corresponding to 3 IU). Addresses above except variability in antibody specificity.

IGF-1 assay

Age and gender reference intervals

General problems with immunoassays: Interferences

Hook effect

Other issues:

Who does dynamic function tests? – laboratory personnel or clinicians

Agreed protocols

Reporting of dynamic function tests