MEDU3400
HUF2-25 Endocrine Tutorial I – Acromegaly
10 October 2023 (Tuesday)
2:30 – 3:15; Group s16A - s16H
3:30 – 4:15; Group s16I - s16P

A 62-year-old man consulted his family doctor because of a 6-month history of severe headache and excessive perspiration. Recently he became aware of changes in his peripheral visual vision and described it as objects disappearing suddenly as if fallen off a cliff. He had suffered from hypertension for 15 years, and occasional shoulder and hand joint pain which were diagnosed as osteoarthritis. Physical examination revealed coarse facial features, enlarged hands and feet, a prominent jaw and bitemporal hemianopia. His BP was 145/105 mmHg and glycosuria was detected. Because of his visual field defect, X-ray imaging of the head was performed and revealed a grossly enlarged pituitary fossa, consistent with a sellar mass.

Biochemical investigations revealed the following:

Plasma analyte	Concentration	Ref. Range
Glucose	8.6 mM	3.5 – 5.5 mM
LH	0.8 IU/L	0.7 – 6.0 IU/L
FSH	1.1 IU/L	<6 IU/L
Prolactin	480 mU/L	<425 mU/L
Testosterone	7.1 nM	10 – 35 nM
GH	9.0 mU/L	<10 mU/L
Cortisol (random)	260 nM	250 – 700 nM
TSH	0.5 mU/L	0.3 – 4.2 mU/L
FT4	10.2 pM	9.4 – 25.0 pM

Questions

1. What is the most likely diagnosis based on the clinical and radiological findings?

2. Suggest why the above biochemical investigations were performed and explain the findings.

A GH suppression test with an oral dose of 75 g glucose (OGTT) was given to this patient and the following results were obtained.

Time (min)	Glucose (mM)	GH (mU/L)
0 (fasting)	7.7	9
30	12.4	12
60	15.7	12
90	13.3	10
120	10.2	11

3. Give reasons for performing this test and interpret the findings.

4. How the clinical presentations of this patient are related to the underlying disorder? Explain your answers.

5. How could this patient be treated?

Suggested reading:
Acromegaly (2019) *Nature Review Disease Primer* Article 20.
https://www.nature.com/articles/s41572-019-0071-6.pdf
Acromegaly (2021) *BMJ Best Practice*
https://bestpractice.bmj.com/topics/en-us/522/pdf/522/Acromegaly.pdf

Suggested answers

1. Headache, loss of peripheral visual field (bitemporal hemianopia) and enlargement of pituitary fossa with a sellar mass would suggest a pituitary tumor extending upward and compressing on the optic chiasma.

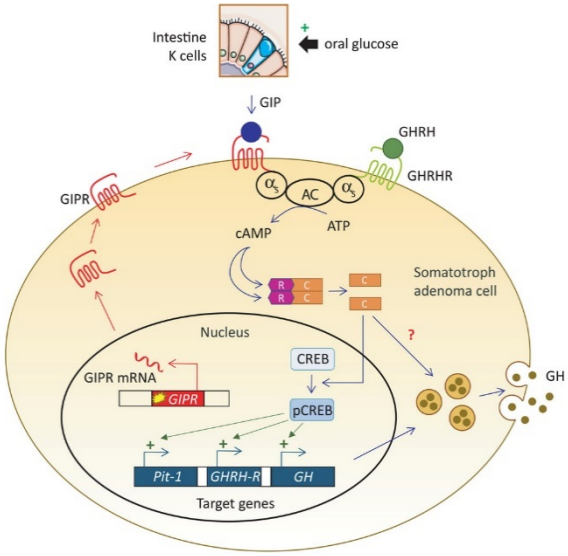
   Coarse facial features, enlarged hands and feet, a prominent jaw, osteoarthritis, hypertension and glycosuria would suggest growth hormone excess.

2. Biochemical investigations were performed to determine:
   (a) Whether the clinical presentation of GH excess would indeed correspond to elevated plasma level of GH.
   (b) Whether the pituitary tumour leads to the development of partial hypopituitarisim due to its mass effect of compressing/damaging the normal pituitary cell types or impairing the hypophyseal portal blood flow in delivering the hypothalamic releasing and inhibiting hormones.
   (c) Whether the glycosuria corresponds to elevated blood glucose level as GH excess leads to insulin resistance, giving rise to hyperglycaemia (and hyperinsulinaemia) and diabetes mellitus.

   The findings could be explained as follow:
   (a) The lack of a significant increase in GH level is related to its pulsatile release with a wide reference range. In normal subjects, most GH secretion occurs at night during Stage III and IV of deep sleep. During daytime, there are few pulses of secretion and GH levels range from undetectable (most of the time) to peak level (given by the value of reference range in the Result Table). The GH data is specially put in to arouse discussion:
   (i) A single random blood measurement is therefore not reliable/representative, especially for GH with a short half-life of around 14 min. Hence there is a need to perform a dynamic test. A GH suppression test with an oral dose of glucose (OGTT) was therefore administered to this patient.
   (ii) Based on the US Endocrine Society guideline (2014), measurement of IGF-1 levels is the first-line biochemical diagnostic test. IGF-1 has a half-life of around 12 hours (versus GH of 20 min). The measured IGF-1 value should be compared with the age- and sex-matched reference range. This would allow a better diagnosis of GH excess if based on a single random blood sample.
   (b) Low LH, FSH and testosterone would suggest that the gonadotrophs are affected by the mass effect of the tumour. Similarly, low TSH and free T_4 indicate the mass effect on thyrotrophs and low cortisol the mass effect on corticotrophs.
   (c) The slight increase in prolactin can be explained by the mass effect of the tumour compressing on to the pituitary stalk, reducing the hypophyseal portal blood supply of prolactin inhibiting hormone – dopamine, since prolactin secretion is under the tonic inhibition of dopamine. The same reasoning can be applied to explain the low LH, FSH and TSH, and these are due to the reduced delivery of hypothalamic releasing hormones (GnRH, and TRH) to the corresponding pituitary cell types to stimulate the synthesis and release of these anterior pituitary hormones.
   It is possible to discuss with students on whether the GH-secreting tumour (adenoma) is co-secreting prolactin. However, it is unlikely for this patient since prolactin should have increased to a much higher plasma concentration (in the order of 2000 mU/ml or above) if it originates from an adenoma.
   (d) The elevated blood glucose level supports the finding of glycosuria, and that the patient should present with diabetes due to anti-insulin effect of excess GH.

3. Since the patient was suspected to have GH excess, therefore a suppression test should be used (hyperglycaemia/OGTT for GH suppression) to determine if the elevated hormone levels were indeed high and would be refractory to suppression.
In normal subjects, GH secretion is suppressed by high blood glucose levels and falls to very low levels (<2 mU/L) within 30 to 120 min in OGTT. Patients with GH-secreting tumour may show inadequate suppression/no suppression (due to autonomous secretion from a pituitary adenoma with the loss of physiological regulation) or a paradoxical increase in GH levels (as in this case).

There are recent findings proposing an explanation to the paradoxical response of GH-secreting pituitary adenoma to an oral dose of glucose. Students have been introduced to this in the lecture. The GH response of the somatotroph adenoma cells to OGTT is due to an overexpression of glucose-dependent insulinotropic polypeptide receptor (GIP-R). In response to an oral dose of glucose, GIP as a member of "incretin" is released from the K cells in the small intestine to amplify glucose-induced insulin secretion. GIP binds GIP-R on adenoma cells to activate a cAMP-signaling pathway, mimicking the mechanism normally triggered by growth hormone releasing hormone (GHRH) to stimulate GH secretion.



4. Clinical presentations related to GH excess and mass effect of the pituitary tumour:
Headache: Mass effect from stretching the dura mater.
Excessive perspiration (hyperhidrosis): Increased growth and activity of the sweat gland
Bitemporal hemianopia/ loss of peripheral visual field: Mass effect of suprasellar compression on the optic chiasma
Enlarged hands and feet, prominent jaw, coarse facial features: Typical appearance in acromegaly from the effect of GH excess.
Osteoarthritis, shoulder and hand joint pain: Hypertrophy and spurring of bone leading to damage of the cartilage
Hypertension: The exact cause is unclear. Several possibilities have been proposed: essential hypertension; increased myocardial contractility due to cardiomegaly; increased proliferation of vascular smooth muscle leading to increased vascular tone; activation of renin-angiotensin-aldosterone system from increased production of angiotensinogen/renin substrate due to hepatomegaly; increased renal sodium and water reabsorption due to nephromegaly.
Glycosuria/ diabetes: Anti-insulin effect of GH.

5. The patient could be treated using medical or surgical means.
Medical treatment (covered in the pharmacology lecture by Prof Alaster Lau):
(a) Octreotide: somatostatin agonist
(b) Cabergoline: dopamine D2 receptor agonist (some GH-secreting tumours are susceptible to inhibition by dopamine agonist, especially for those co-secreting prolactin)
(c) Pegvisomant: a GH receptor antagonist

Surgical treatment: hypophysectomy (removal of the pituitary gland with the tumour)

Irradiation (gamma knife, external beam)