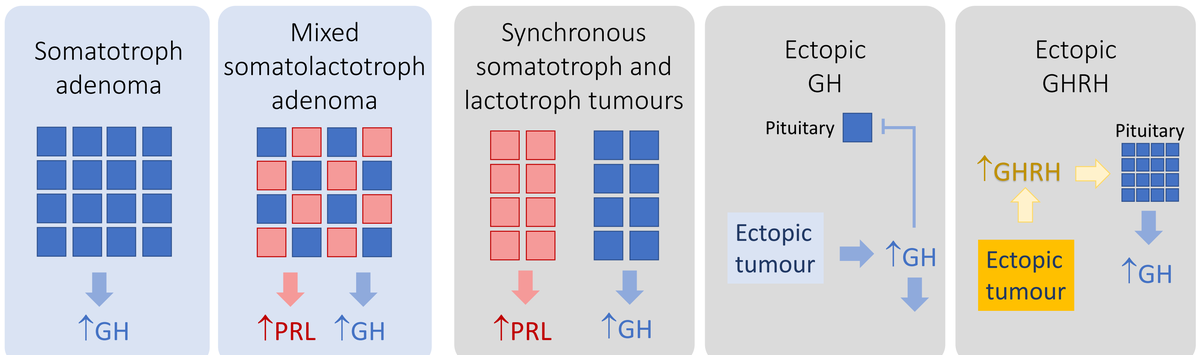
Clinical and biochemical acromegaly associated with pituitary gonadotroph adenomas

Isabel Huang-Doran[1,2,*], Olympia Koulouri[1,2,*], Sue Oddy[2], David Halsall[2], Dominic G O'Donovan[2], Richard J Mannion[2], Federico Roncaroli[3], Kieren Allinson[2], Mark Gurnell[1,2]

[1]University of Cambridge Metabolic Research Laboratories, Wellcome-MRC Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK.
[2]Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, UK. [3]Division of Neuroscience and Experimental Psychology, Faculty of Medicine, University of Manchester, Manchester, UK.

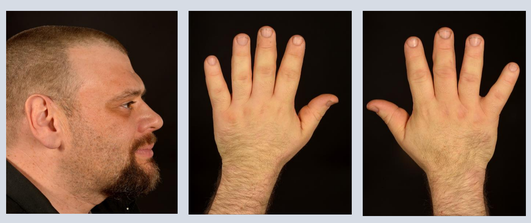
Introduction

- Acromegaly is a clinical manifestation of excessive peripheral growth hormone (GH) action. The vast majority of cases result from somatotroph adenomas of the pituitary. These tumours display varying degrees of GH immunoreactivity. They also express the somatotroph lineage-determining transcription factor Pit-1.
- Occasionally, GH is co-secreted with a second adenohypophyseal hormone from adenomas containing mixed cell populations within the same lineage (e.g. somatolactotroph tumours).
- Co-existence of multiple discrete adenomas, identical or distinct in their hormone secretion, is infrequent (1-2).
- In very rare cases, acromegaly results from neuroendocrine tumours producing ectopic growth hormone-releasing hormone (GHRH) or GH (3-5).
- Gonadotroph adenomas are typically non-functional. Rarely, FSH-producing adenomas cause hormonal hypersecretion syndromes such as ovarian hyperstimulation, testicular enlargement, and precocious puberty (6-8).

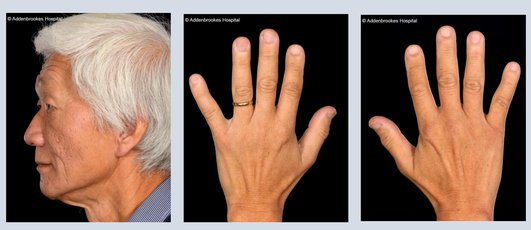


Clinical cases

Patient 1
- 39 year-old male.
- Presentation: visual disturbance. Bitemporal hemianopia noted on ophthalmic assessment.
- Clinical features of acromegaly with macro-orchidism.
- No background of diabetes, hypertension, carpal tunnel syndrome or sleep apnoea. No renal/liver disease.
- MRI pituitary: macroadenoma with suprasellar extension, displacing the optic chiasm.



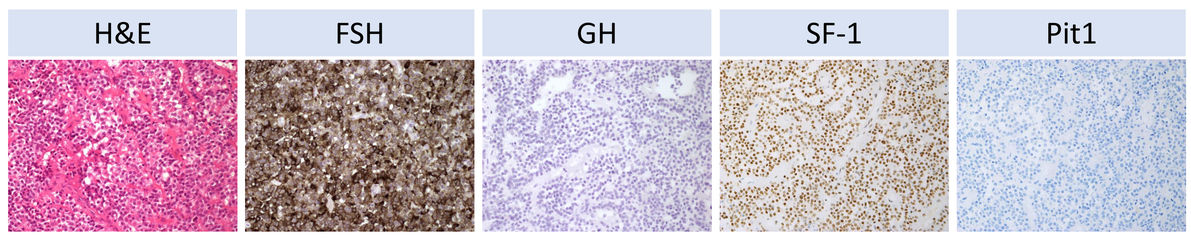
Patient 2
- 66 year-old male.
- Presentation: headache with acute loss of vision in the left eye.
- Background of diabetes (HbA1c 55mmol/mol), hypertension, sleep apnoea.
- MRI: large cystic pituitary macroadenoma with supresellar extension and chiasmal compression.
- Mild features of acromegaly noted post-operatively.



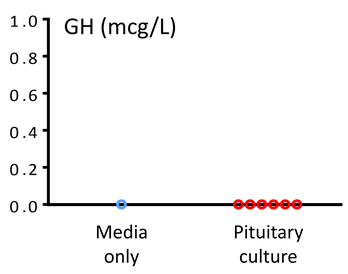
Patient 3
- 73 year-old male.
- Presentation: vertigo. Clinical concern of stroke.
- PMH: sleep apnoea, hypertension, carpal tunnel syndrome.
- MRI: incidental heterogeneous pituitary mass, displacing the infundibulum to the left.
- Clinical features of acromegaly. No visual field deficit.

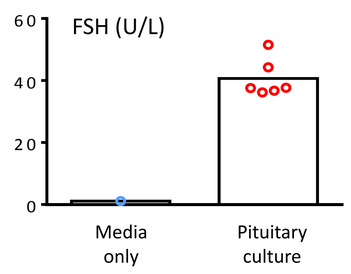
Histology

Representative immunohistochemistry (P1, TSS 2)



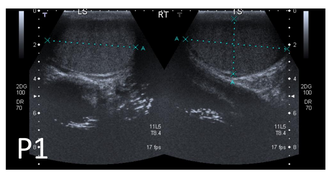
Patient	Tissue source	Cambridge			Manchester				
		GH	FSH	LH	GH	FSH	LH	SF-1	Pit-1
P1	TSS 1	Negative	Positive	Sparse					
	TSS 2	Negative	Positive	Negative	Negative	Positive	Some	Positive	Negative
P2	TSS 1	Negative	Positive	ND					
	TSS 2	Negative	Positive	Scanty	Negative	Positive	Some	Positive	Negative
P3	TSS 1	Negative	Positive	Negative	Negative	Positive	Some	Positive	Negative
	Lung nodule	Negative	Negative	Negative					

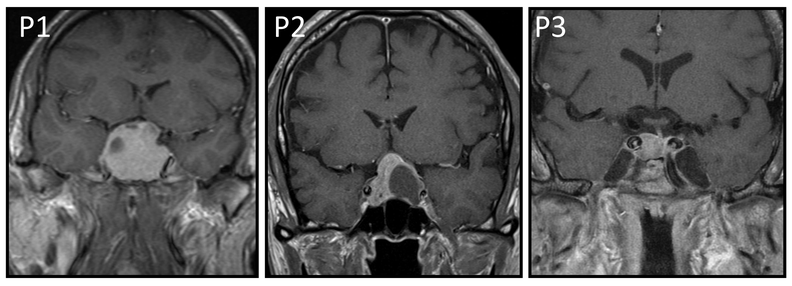




GH and FSH secreted by primary pituitary cultures from Patient 1. Samples of resected pituitary adenoma (from TSS 2) were subject to trypsin digestion then plated in culture media supplemented with hormone-stripped serum. After 24 hours media was collected, cell debris removed by centrifugation and anterior pituitary hormone levels quantified using standard clinical immunoassays.

Biochemical and radiological workup



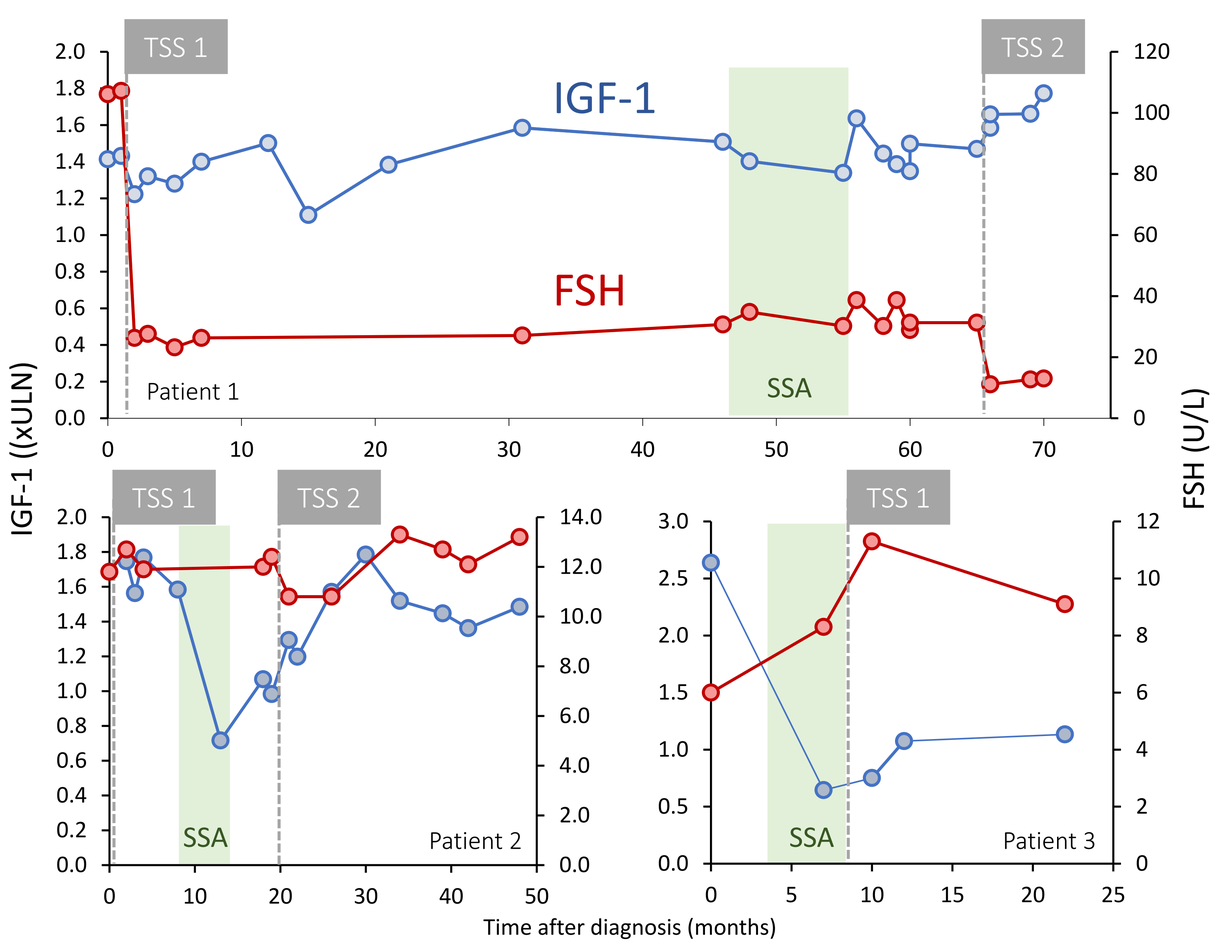


Above: Testicular ultrasound in P1 showing 46ml (left) and 50ml (right) testes without neoplasia.
Right: Pre-operative MRI scans in patients P1-P3. T2 weighted images with gadolinium.

Biochemistry	Ref Range	P1	P2	P3
Age (years)		39	66	73
Presentation		Bitemporal hemianopia	Monocular blindness, headache	Vertigo
Clinical features		Acromegaly, macro-orchidism	Acromegaly, T2DM, hypertension, OSA	Acromegaly, hypertension, OSA
IGF-1 (nmol/L)		64.4 (9.5-45.0)	51.2 (12.7-29.3)	77.3 (12.7-29.3)
IGF-1 (xULN)		1.4	1.7	2.6
GH (mcg/L)[1]	*Basal*	1.5	2.4	5.6
	Nadir	**1.2**	**2.4**	**7.6**
FSH (U/L)	[1.0-10.7]	**107**	**11.8**	9.0
LH (U/L)	[1.5-6.3]	1.2	4.2	6.2
Testosterone (nmol/L)	[8.0-29.0]	9.3	7.2	8.3
Prolactin (mU/L)	[45-375]	370	355	124
Cortisol (nmol/L)[2]	*0 mins*	429	386	423
	30 mins	666	522	722
TSH (mU/L)	[0.35-5.50]	0.65	1.94	1.69
Free T4 (pmol/L)	[10.0-19.8]	12.3	14.6	16.1
GHRH immunoassay		Not detected	Not detected	Not detected
Radiology		P1	P2	P3
Cross sectional imaging (CT chest, abdomen & pelvis)		No significant abnormality	No significant abnormality	1cm nodule right lower lobe[3]
Functional imaging		-	**Octreotide scan:** No pathological uptake **FDG PET:** Uptake in prostate[4]	**FDG PET:** No pathological uptake
Response to somatostatin analogue (% reduction in IGF-1)		11%	54% (intolerant)	76%

[1]Assessed during a 75g oral glucose tolerance test. [2]Assessed during a Synacthen test. [3]Subsequently confirmed to be a lung adenocarcinoma. [4]Subsequently confirmed to be a Gleeson 3+3=6 prostatic adenocarcinoma.

Serial follow-up



Summary / Conclusions

- **We describe three patients with clinical and biochemical acromegaly associated with pituitary gonadotroph adenomas and variable elevation in circulating FSH.**
- All tumours were immunoreactive for FSH and SF-1 only (5 samples from 3 patients).
- No patients had evidence of somatotroph adenomas or hyperplasia.
- No ectopic source of GH secretion was identified, and GHRH was negative in all three patients.
- Two patients showed a biochemical response to somatostatin analogue therapy.
- Two patients have persistent post-operative IGF-1 hypersecretion.

References: *(1) Sano T et al. Pituitary. 1999 May;1(3-4):243-50. (2) Kontogeorgos G et al. Neurosurgery. 1992 Nov;31(5):840-9. (3) Faglia G et al. Endocrinol Metab Clin North Am. 1992 Sep;21(3):575-95. (4) Doga M et al. Ann Oncol. 2001;12 Suppl 2:S89-94. (5) Ghazi AA et al. Endocrine. 2013 Apr; 43(2): 293–302. (6) Clemente M et al. Horm Res Paediatr. 2011;75(3):225-30. (7) Wang X et al. Int J Fertil Steril. 2014 Apr-Jun; 8(1): 99–104. (8) Vargas G et al. Endocrinol Diabetes Metab Case Rep. 2017: 17-0057.* Funding: *NIHR Academic Clinical Fellowship (IHD), Cambridge NIHR Biomedical Research Centre.*

BES2018 8--CC
Neuroendocrinology and pituitary
Isabel Huang-Doran
Poster presented at: SfE BES 2018 19-21 November GLASGOW
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