Pituitary hyperplasia: case series and literature review of an under-recognised and heterogeneous condition

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Summary

Pituitary hyperplasia (PH) occurs in heterogeneous settings and remains under-recognised. Increased awareness of this condition and its natural history should circumvent unnecessary trans-sphenoidal surgery. We performed an observational case series of patients referred to a single endocrinologist over a 3-year period. Four young women were identified with PH manifesting as diffuse, symmetrical pituitary enlargement near or touching the optic apparatus on MRI. The first woman presented with primary hypothyroidism and likely had thyrotroph hyperplasia given prompt resolution with thyroxine. The second and third women were diagnosed with pathological gonadotroph hyperplasia due to primary gonadal insufficiency, with histopathological confirmation including gonadal-deficiency cells in the third case where surgery could have been avoided. The fourth woman likely had idiopathic PH, though she had concomitant polycystic ovary syndrome which is a debated cause of PH. Patients suspected of PH should undergo comprehensive hormonal, radiological and sometimes ophthalmological evaluation. This is best conducted by a specialised multidisciplinary team with preference for treatment of underlying conditions and close monitoring over surgical intervention.

Learning points:

- Normal pituitary dimensions are influenced by age and gender with the greatest pituitary heights seen in young adults and perimenopausal women.
- Pituitary enlargement may be seen in the settings of pregnancy, end-organ insufficiency with loss of negative feedback, and excess trophic hormone from the hypothalamus or neuroendocrine tumours.
- PH may be caused or exacerbated by medications including oestrogen, GNRH analogues and antipsychotics.
- Management involves identification of cases of idiopathic PH suitable for simple surveillance and reversal of pathological or iatrogenic causes where they exist.
- Surgery should be avoided in PH as it rarely progresses.

Background

Pituitary hyperplasia (PH) is defined as an absolute increase in the number of one or more adenohypophyseal cell subtypes, manifesting radiologically as pituitary enlargement beyond what is considered normal (1).

Histological hallmarks of PH include a polymorphic, hypercellular population with enlarged acini and an intact reticulin network (2). Much of what is known has been derived from studies of *in toto* pituitaries obtained at

autopsy. In contrast, pituitary biopsy is hampered by regional variation in cell subtypes together with poor anatomic localisation of surgical specimens; frequent surgical compression artefact with loss of identifying hormonal antigens; and inter-individual variability in cell counts and distribution (3). Furthermore, surgical management is rarely indicated, thus the diagnosis of PH remains predominantly clinical, hormonal and radiological. Classic features on MRI include diffuse and symmetrical pituitary enlargement, isointensity to grey matter, and homogenous gadolinium uptake (4).

Herein we present a case series of four patients with hyperplasia of the pituitary: three resulting from target organ insufficiency and the fourth idiopathic. One patient had a tissue diagnosis, whilst the diagnosis in the other patients was based on clinical, hormonal and radiological findings.

The epidemiology of PH is not clearly defined and there are no guidelines to aid assessment and management. We argue, on the basis of four cases presenting over a 3-year period, that it is a sufficiently frequent presentation to warrant attention.

Case presentation

Four young women presented with PH with no family history of pituitary disease or endocrine neoplasia. Distinctly, in all cases, MRI demonstrated diffuse and symmetrical pituitary enlargement with homogenous gadolinium enhancement. Visual field perimetry was normal in each case.

Patient 1

Patient 1, aged 19, presented with abdominal pain and diarrhoea and was found to have profound primary hypothyroidism with elevated thyroid-stimulating hormone (TSH) of 660 mIU/l and undetectable free thyroxine (fT_4). Anti-thyroid peroxidase antibody was elevated, consistent with autoimmune thyroid disease. Further questioning uncovered a history of mild headaches, fatigue, expressible galactorrhoea, clouded thinking, cold intolerance and gradual weight gain. Investigations revealed mild renal impairment, liver dysfunction, normocytic anaemia, and a low-voltage electrocardiogram, all attributed to severe hypothyroidism. Her father had a history of myxoedema coma. Her general practitioner ordered an MRI brain, which revealed pituitary enlargement to a height of 13 mm with suprasellar extension in contact with the optic chiasm (Fig. 1A). She was diagnosed with pathological thyrotroph

hyperplasia due to primary hypothyroidism. Subsequent pituitary profile revealed elevated growth hormone (GH) and low insulin-like growth factor 1 (IGF1), and mild hyperprolactinaemia (Table 1) likely related to pituitary stalk compression or lactotroph hyperplasia stimulated by thyrotrophin-releasing hormone (TRH).

Symptoms resolved promptly with T_4. TSH normalised after 2 months and repeat MRI at 3 months showed shrinkage of the pituitary to 8.5 mm (Fig. 1B).

Patient 2

Patient 2, aged 35, presented with 9 months of secondary amenorrhoea and headaches. Investigations revealed low-normal oestradiol and marked elevation
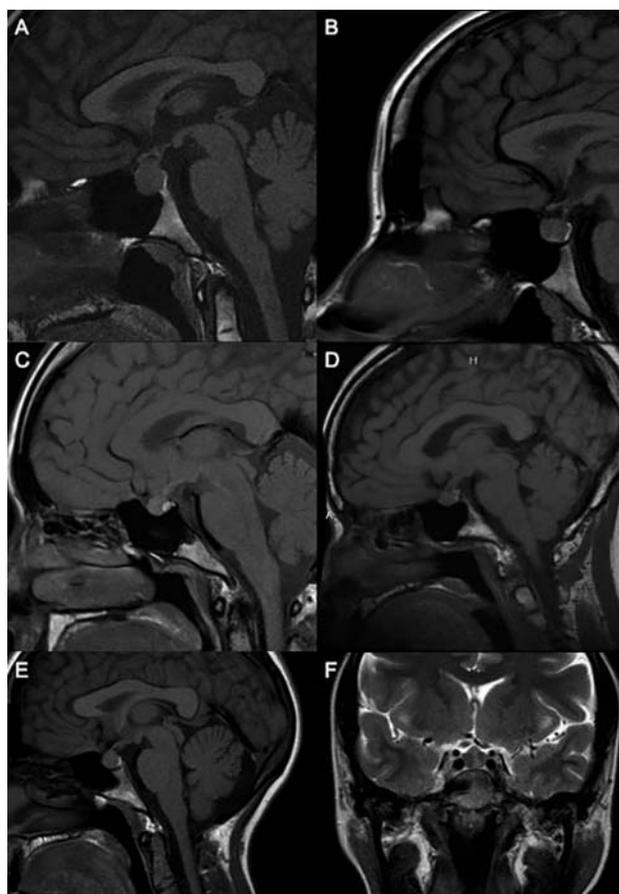

Figure 1

Corresponding T1-weighted non-contrast sagittal MRI slices of Patient 1 at baseline (A) and follow-up (B) showed reduction in pituitary size and resolution of suprasellar extension after 3 months of T_4. Baseline non-contrast MRI slices demonstrated diffuse pituitary enlargement, suprasellar extension and loss of superior concavity in Patients 2 (C) and 3 (D) on T1-weighted sagittal views, and in Patient 4 on T1-weighted sagittal (E) and T2-weighted coronal views (F).

Table 1 Morning pituitary profile at referral with abnormal results in bold.

Blood test	Patient 1	Patient 2	Patient 3	Patient 4	Reference[a]	Unit
ACTH	10.7	5.7	2.4	5.3	[1–3]0–12 [4]<11	pmol/l
Cortisol	477	524	228	**470**	[1,3]70–650 [2]138–650 [4]100–400	nmol/l
TSH	**566**	1.77	0.82	1.0	[1–3]0.40–3.50 [4]0.5–4.5	mIU/l
FT$_4$	**3.0**	14.3	13.4	10	[1–3]9–19 [4]10–20	pmol/l
FT$_3$	**1.6**	3.9	–	–	[1,2]2.6–6.0	pmol/l
GH	**26.8**	8.1	2.0	**27**	[1]0–10 [2,3]0–15 [4]0–18	mIU/l
IGF1	**13.4**	23	31	24	[1]16–55 [2,3]14–37 [4]17–42	nmol/l
FSH	7.7	**68.5**	**74.0**	6		IU/l
LH	8.3	**30.1**	**38.5**	7.8		IU/l
Oestradiol	117	**195**	**<37**	91		pmol/l
Progesterone	–	**<1.0**	–	1		nmol/l
Prolactin	**782**	178	175	148	[1–3]85–500 [4]40–570	mIU/l

ACTH, adrenocorticotrophin hormone; TSH, thyroid-stimulating hormone; fT$_4$, free thyroxine; fT$_3$, free triiodothyronine; GH, growth hormone; IGF1, insulin-like growth factor 1; FSH, follicle-stimulating hormone; LH, luteinising hormone.
[a]Reference intervals are given for each patient with superscript indicating patient number.

of gonadotrophins (Table 1). Other pituitary hormones were normal. MRI pituitary revealed an enlarged pituitary measuring 10.5 mm in height with superior convexity and suprasellar extension approaching the optic chiasm (Fig. 1C). She was diagnosed with pathological gonadotroph hyperplasia due to premature ovarian failure (POF).

Upon review 7 months later, the patient reported return of menses for 3 months with a healthy oestradiol of 662 pmol/l and mid-range gonadotrophins. Pituitary size was unchanged on repeat MRI. Ovarian ultrasound demonstrated a few small follicles and fertility options, including oocyte donation and *in vitro* fertilisation, were discussed along with the likely need for oestrogen replacement in the future.

Patient 3

Patient 3 presented at the age of 35 with visual changes and headaches on a background of ovarian cancer for which she underwent bilateral salpingo-oophorectomy and chemotherapy 2 years prior. MRI brain revealed pituitary enlargement measuring 9 mm in height with suprasellar extension abutting the optic chiasm (Fig. 1D). Hormonal evaluation demonstrated menopausal-range gonadotrophins and undetectable oestradiol consistent with surgical menopause and the absence of oestrogen

replacement (Table 1). Other pituitary hormones were normal. Upon neurosurgical review, she was diagnosed with a non-functioning pituitary macroadenoma and proceeded to trans-sphenoidal surgery. Histopathology demonstrated signs of pathological gonadotroph hyperplasia including gonadal-deficiency cells (Fig. 2).

Perioperatively, the patient had a chest X-ray revealing multiple cystic pulmonary lesions and a unilateral pleural effusion. Biopsy confirmed metastatic recurrence of ovarian adenocarcinoma. Review of pituitary tissue showed no evidence of metastasis.

Patient 4

Patient 4 presented aged 28 years with tinnitus, but no features to suggest pituitary disease. MRI brain revealed an enlarged pituitary measuring 13 mm in height with suprasellar extension near the prechiasmatic optic nerves (Fig. 1E and F). Pituitary hormones were unremarkable apart from raised GH with normal IGF1, and minimal elevation of cortisol (Table 1). She had no mass effect symptoms, recent gestational history, personal or family history of autoimmunity or systemic features to suggest hypophysitis and serum angiotensin-converting enzyme was normal. She was diagnosed with idiopathic PH and serial imaging after 13 months was unchanged.
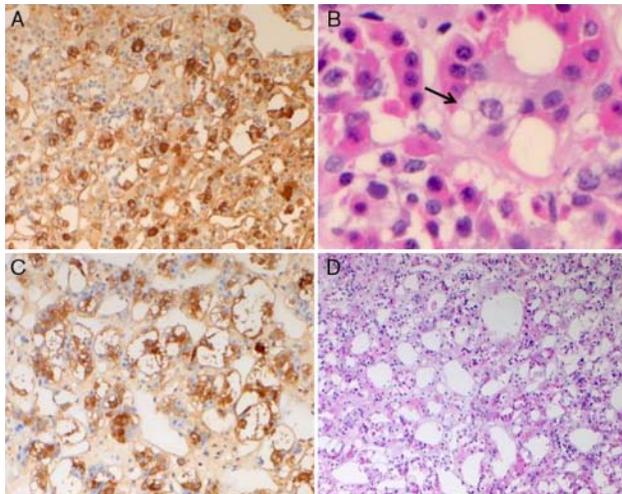
Figure 2

Trans-sphenoidal surgical specimens of Patient 3 demonstrated high gonadotroph concentration on FSH staining at 200× magnification (A) and gonadal-deficiency cells with pale, vacuolated cystoplasm on haematoxylin & eosin staining at 400× magnification (B, arrow). LH staining at 200× magnification (C) revealed the vacuolated cells to be enlarged gonadotrophs with eccentrically displaced nuclei producing a signet-ring appearance in some areas. The gland appeared porous with distended vascular spaces on haematoxylin & eosin staining at 100× magnification (D), possibly reflecting increased vascular demand by the hyperplastic pituitary. There was no acinar enlargement on silver staining for reticulin (not shown). FSH, follicle-stimulating hormone; LH, luteinising hormone.

The patient had previously been diagnosed with polycystic ovary syndrome (PCOS) with oligomenorrhoea, hyperandrogenism and polycystic ovaries on ultrasound. She was treated with the oral contraceptive pill until age 23. At the time of pituitary imaging, there was ongoing clinical evidence of PCOS and she desired pregnancy.

Discussion

'Normal' pituitary dimensions have been empirically defined from limited radiological studies. It is believed that idiopathic pituitary enlargement beyond these dimensions is a rare phenomenon (1).

An MRI study (5) of 1020 subjects with no suspicion of pituitary disease found that mean pituitary height in females was greater than in males (5.35 mm vs 4.93 mm, $P < 0.0001$). Height peaked in the 20–29 year-old age group (female 6.48 mm, male 5.63 mm) and subsequently declined with age, except amongst females where there was a small increase in the 50–59 year-old age group (5.44 mm) coinciding with menopause. The authors concluded that pituitary height should be <9 mm in

patients aged 20–29 years and <8 mm in other age groups as only one subject fell outside these ranges. Such thresholds may suggest pathology in otherwise healthy individuals as demonstrated in a case series reported by Chanson et al. (4) of seven women with pituitary heights measuring 9–12 mm in the absence of endocrinopathy. In our series, Patient 4 had a pituitary height of 13 mm, well above what is considered normal. No endocrinopathy was found, except perhaps for PCOS, and thus she is believed to have 'idiopathic' PH although PCOS is a theoretical cause as discussed in the next section.

Physiological hyperplasia

In addition to youth and menopause, physiological PH occurs during pregnancy where lactotrophs rise from a basal contribution of 10–30% of adenohypophyseal cells up to 70% around term (3). This does not completely reverse (2), explaining increased pituitary volumes in multiparous compared to nulliparous women (1). Gestational lactotroph hyperplasia likely occurs via maturation of pluripotent pituitary cells, proliferation of mature lactotrophs and transdifferentiation of other pituitary cells, especially somatotrophs (2). The minimal mitotic activity seen in hyperplastic pituitaries argues for a strong contribution of the latter (1).

An MRI study of 78 pregnant women and 18 controls found that pituitary height progressively increased during pregnancy, and peaked immediately *postpartum* (mean 8.76 mm, maximum 10.2 mm) before normalising by 2–6 months (6). Another radiological study of healthy pregnant women found maximum heights of 10.0 mm in pregnancy and 11.8 mm *postpartum* (7). Therefore, pituitary heights up to 10 mm during pregnancy and 12 mm immediately *postpartum* may be considered physiological. As in our case series, PH appears to occur more frequently in young women. The degree to which pregnancy may exacerbate underlying PH is unclear.

In the elderly, the well described 'basophil invasion' of pars intermedia-derived pro-opiomelanocortin (POMC) cells into the neurohypophysis may be mistaken for a tumour, however it is considered a non-functional normal variant of PH (2).

Pathological hyperplasia

End organ insufficiency

Pathological PH is classically due to end organ insufficiency, particularly primary hypothyroidism. Thyrotroph

hyperplasia is well documented, particularly in young females, and may even cause chiasmal compression (8). Surgery is rarely indicated due to prompt reversal with T$_4$ (8), as demonstrated in Patient 1. Thyrotroph counts are inversely related to somatroph populations in thyrotroph hyperplasia (3), and propylthiouracil-treated rats develop reversible transdifferentiation of somatotrophs into thyrosomatrophs suggesting cellular plasticity as a major underlying mechanism (9). Thyrotroph hyperplasia may be accompanied by lactotroph hyperplasia induced by TRH (8), which might explain the hyperprolactinaemia and galactorrhoea observed in Patient 1.

Primary hypogonadism of any aetiology may produce gonadotroph hyperplasia (10) and sellar expansion has been noted in patients with Klinefelter's and Turner's syndromes (11). Pituitary enlargement around the time of menopause is followed by a decline in height after 60 years of age suggesting gonadotroph hyperplasia may resolve over years (5). There are no modern radiological studies showing pituitary shrinkage with normalisation of sex steroid levels in POF to advise the expected timing of resolution in Patient 2.

Histological diagnosis of gonadotroph hyperplasia is challenging due to the wide range in number and diffuse dispersion of gonadotrophs. Diagnosis may be obtained, however, by identification of pathognomonic gonadal-deficiency cells with enlarged, vacuolated cytoplasm occasionally yielding a signet-ring appearance (2) (3), as seen in Patient 3. Such cellular change is readily documented in gonadal dysgenesis (12), but it is uncommon following gonadectomy and rare in postmenopausal women (10). Gonadotroph hypercellularity has occasionally been found (10) (12), however definitive acinar enlargement has not been described to our knowledge. In our case, pituitary enlargement was attributed to increased gonadotroph number and size as well as gland hypervascularity.

PCOS, another primary gonadal pathology, has also been cited as a cause of gonadotroph hyperplasia (13) and may be implicated in Patient 4 and in two of the seven patients reviewed by Chanson *et al.* (4). It is speculated that the luteinising hormone (LH) excess of PCOS may be related to dopaminergic insufficiency whereby concomitant disinhibition of lactotrophs might explain the frequent coexistence of hyperprolactinaemia and potential lactotroph hyperplasia (14). Other cell subtypes may be involved in PCOS-associated PH as transgenic mice overexpressing LH show proliferation of the *PIT1* lineage including lactotrophs, somatotrophs and thyrotrophs (15). The high frequency of PCOS with few reports of

pituitary enlargement argues for additional environmental or hormonal factors. Furthermore, thyrotroph hyperplasia has been described together with polycystic ovaries in primary hypothyroidism due to homology between the alpha-subunits of TSH and follicle-stimulating hormone (FSH) (16).

Other cell lines are less commonly affected by end organ insufficiency. Corticotroph hyperplasia rarely occurs in primary adrenal insufficiency (17), perhaps because of the rapid detection of hypocortisolism. A case series (18) of patients with Laron dwarfism characterised by GH resistance resulting in low levels of IGF1 found no evidence of pituitary enlargement suggesting that somatotrophs do not proliferate in the absence of negative feedback.

Mutations in the pituitary transcription factor gene, *PROP1*, may also result in pituitary hormone insufficiency and transient pituitary enlargement, however this is usually identified by combined pituitary hormone deficiency involving GH, prolactin, TSH, LH, FSH and rarely adrenocorticotrophin hormone (19).

Excess trophic hormone

Somatotroph or corticotroph hyperplasia may arise due to ectopic secretion of GH-releasing hormone (GHRH) or corticotrophin-releasing hormone, respectively, mimicking functional adenomas (20) (21). Upregulation of hypothalamic GHRH is a suspected cause of rare cases of mammosomatotroph hyperplasia manifesting as congenital gigantism (3).

Iatrogenic hyperplasia

Oestrogen

Oestrogen excess stimulates lactotroph proliferation and pituitary enlargement in rat models (22). The mechanism is likely multifactorial including antagonisation of the inhibitory effect of dopamine on the pituitary (2). Oestrogen may hence produce PH in humans theoretically, and prolactinomas have been described in male-to-female transgender patients administered oestrogen (23). A retrospective study found no association between the oral contraceptive pill and prolactinoma (24), but the possibility of lactotroph hyperplasia has not been explored. In addition, a synergistic effect on pituitary size in women with PCOS taking the oral contraceptive pill has not been examined, which may be of relevance for Patient 4.

Assisted reproductive technologies

Gonadotrophin-releasing hormone analogues may have a transient stimulatory effect on gonadotrophs that are already hyperplastic or neoplastic. This was noted in a case report (25) of a woman with subfertility and spontaneous ovarian hyperstimulation where leuprolide downregulation prior to planned ovulation induction resulted in worsening ovarian cysts and oestradiol levels. She was subsequently found to have a gonadotroph adenoma. This is of concern for women with hyperplastic pituitaries in the setting of PCOS or POF as they frequently require assisted reproductive technologies, as considered by Patient 2.

Antipsychotics

Dopamine D2 receptor-knockout mice develop lactotroph hyperplasia and prolactinomas (26). In humans, antipsychotic use correlates with larger pituitary volumes compared to controls, and hyperprolactinaemia is frequently seen (27). Post-marketing data of antipsychotics illustrate an association with pituitary tumours (28), suggesting that this class of drugs may contribute to a hyperplasia-adenoma sequence.

Hyperplasia-adenoma sequence

Adenoma is probably not a frequent consequence of hyperplasia as there is no increase in prolactinoma incidence in multiparous women (1). Adenoma formation is still occasionally observed in the setting of hyperplasia of somatotrophs, lactotrophs, corticotrophs and thyrotrophs (3). End organ insufficiency has been documented in some cases suggesting it may be an inciting factor in the hyperplasia-adenoma sequence (12). An impressive example is bilateral adrenalectomy for Cushing's disease whereby loss of negative feedback may induce Nelson's syndrome with PH and/or adenoma formation (1). Excess POMC-derived endorphin and galanin produced by tumourous corticotrophs may also stimulate lactotroph hyperplasia (1) (3). Alternatively, any adenoma disrupting infundibular dopamine transport may cause disinhibition of lactotroph proliferation (3).

McCune–Albright syndrome and Carney complex classically involve somatotroph hyperplasia sometimes culminating in neoplasia (20), however other genetic factors are less understood. Though pancreatic lesions in multiple endocrine neoplasia type 1 frequently contain hyperplasia alongside adenoma, this is uncommon in the pituitary (29). Recently, non-identical twin sisters were found to have somatotrophinomas in association with somatotroph hyperplasia, and genetic sequencing revealed germline mutations in the aryl hydrocarbon receptor interacting protein (*AIP*) gene in both girls (30). *AIP* sequencing of the pituitary specimens revealed loss-of-heterozygosity in tumour tissue, but not hyperplasic areas, implicating a 'second hit' in tumour formation.

Conclusion

We advocate that patients presenting with pituitary enlargement greater than predicted by age, gender and physiological state, undergo complete endocrinological assessment and MRI pituitary with gadolinium. Visual field perimetry should be obtained if the gland approaches or contacts the optic apparatus. We believe an experienced multidisciplinary team is best positioned to identify and manage PH. In addition, we speculate that the 'normal' pituitary gland has a wider range in size than previously recognised. Hasty surgery is to be avoided with priority given to comprehensive evaluation, management of inciting factors and careful monitoring.

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