Pituitary Function at Presentation and Following Therapy in Patients with Non-functional Pituitary Adenomas: A Single Centre Retrospective Cohort Study

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Abstract

Background:
Non-functioning pituitary macroadenomas (NFPMs) may present with hypopituitarism. Pituitary surgery and radiotherapy pose an additional risk to pituitary function.

Objectives
To assess the incidence of hypopituitarism at presentation, the impact of treatment, and the likelihood of endocrine recovery during follow-up.

Methods
All patients treated surgically with and without radiotherapy for NFPMs between 1987 and 2018 who had longer than 6 months follow-up were identified. Demographics, presentation, investigation, treatment, and outcomes were collected.

Results
In total, 383 patients were identified. The median age was 57 years with a median follow-up of 8 years. Preoperatively, 235 patients (235/377; 62%) had evidence of at least one pituitary deficiency. Anterior panhypopituitarism was more common in men (p =0.001), older patients (p =0.005), and in those with adenomas extending beyond the sella turcica (p =0.05). Patients treated with surgery and radiotherapy had a higher incidence of all individual pituitary hormone deficiency and anterior panhypopituitarism as well as significantly lower GH, ACTH, and TSH deficiencies free survival probability than those treated with surgery alone. Recovery of central hypogonadism, hypothyroidism, and anterior panhypopituitarism was also less likely to be reported in those treated with surgery and radiotherapy.

Conclusion
NFPMs are associated with significant degree of hypopituitarism at time of diagnosis and post therapy. The combination of surgery and radiotherapy is associated with higher risk of pituitary dysfunction. Recovery of pituitary hormone deficit may occur after surgical treatment. Patients should have regular ongoing endocrine evaluation post-treatment to assess changes in pituitary function and the need for long-term replacement therapy.

Introduction
Non-functioning pituitary adenomas are benign tumours of the adenohypophysis with gonadotropin expressing subtype accounting for up to 80% of these tumours<sup>1–3</sup>. These neoplasms vary in clinical presentation from an incidental finding on neuroimaging to large macroadenomas (NFPMs) damaging the pituitary gland, optic apparatus, and surrounding neurological structures<sup>4,5</sup>. Hypopituitarism can be
the presenting manifestation in many patients; however, the process of developing hormones deficiency is often latent and asymptomatic.

The risk of developing partial and complete hypopituitarism in patients with NFPMs is increased after surgical resection and radiotherapy. Moreover, in selected patients there is recovery of pituitary function. Longterm and regular screening for hypothalamic-pituitary insufficiency after NFPMs treatment is therefore of crucial importance to provide appropriate replacement therapy and to prevent short and long term patient morbidity and mortality\(^6\text{–}^8\).

In this study, we investigated the course of pituitary dysfunction in NFPMs following surgical resection with and without radiotherapy. The aims were to assess the incidence of hypopituitarism pre-operatively in patients with NFPMs and following surgery with and without radiotherapy, and the likelihood of recovery of pituitary function post treatment during follow up.

**Methods**

Ethics approval to conduct this study was obtained from Westminster Research Ethics Committee on 07/04/2020. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was used in the preparation of this section of the manuscript\(^9\). This study was conducted as a single centre cohort study. It included all patients who underwent surgical resection for non-functioning pituitary macroadenomas between 1987 and 2018 with a follow up duration of more than six months. The study was conducted at the National Hospital for Neurology and Neurosurgery in London, one of the busiest neurosurgical centres and the largest pituitary centre in the United Kingdom. Surgical resection was performed mainly by three experienced neurosurgeons (MP, JG and ND). A retrospective review of electronic case notes was performed.

**Data collection**

Data on patients' demographics, clinical presentation, treatment modalities and details of endocrine testing were collected.

The diagnosis of NFPMs was based on the absence of clinical and biochemical evidence of pituitary hormone hypersecretion and/or expression of pituitary adenoma markers on immunohistological analysis of surgically resected pituitary specimens. Patients in our centre had full pituitary evaluation preoperatively and received appropriate pituitary hormone replacement during the immediate postoperative period. In each case, patients underwent full endocrine assessment including dynamic testing if indicated at 6-8 weeks after surgery, and at least yearly thereafter during follow-up. For those treated with radiotherapy dynamic testing was done approximately one year after irradiation and when indicated thereafter during follow-up.

Patients with severe growth hormone (GH) deficiency on provocative testing (peak GH response < 3 µg/dL) or those on GH treatment were defined as GH-deficient. Patients with combined thyroid
stimulating hormone (TSH), adrenocorticotropic hormone (ACTH) and gonadotropins deficiencies without a dynamic test were also considered deficient in GH. Patients with ACTH and TSH deficiencies were reported deficient when patients received glucocorticoid and thyroxine therapy, respectively. In addition, patients who had low morning cortisol level of less than 100 nmol/L and those with suboptimal response to dynamic testing were recorded ACTH deficient and those with low free T4 level with inappropriately normal or low TSH level were TSH deficient. Patients with primary hypothyroidism were not considered having TSH dysfunction. Gonadotrophin deficiency was defined as follows: men were deficient if they were receiving testosterone therapy or if early morning testosterone level was low in the presence of inappropriately normal or low serum gonadotrophins. Premenopausal women with amenorrhoea and inappropriately normal or low serum gonadotrophins were recorded as having hypogonadotrophic hypogonadism, while those women received oestrogen replacement in the form of hormone replacement therapy were also considered to be deficient in gonadotrophins depending on their other pituitary deficiencies. Postmenopausal women with non-elevated serum gonadotrophins were also documented gonadotrophin deficient. Anterior hypopituitarism was considered when there was a loss of three or more anterior pituitary hormones. Patients on desmopressin replacement therapy were considered to have central diabetes insipidus.

Recovery of pituitary function was considered when there was normalisation of the deficient hormones either on basal endocrine evaluation or dynamic testing at any point during after surgery or radiotherapy and in the case of anterior panhypopituitarism if total anterior pituitary hormone deficit recovered to less than three.

Statistical analysis

Basic data were evaluated using descriptive statistics. Mean and standard deviation (SD) were used to describe continuous variables. Median and interquartile range (IQR) were used to describe data not normally distributed. Exact Fisher’s test was used to compare categorical variables including the trend in postoperative sodium level. Hypopituitarism free survival probability curves were generated by Kaplan–Meier method and the evaluations of the differences in the various sub-groups done by the log-rank test. Spearman analysis test was used to measure the associated between continuous and nominal variables. IBM SPSS statistics version 28 was used in this study.

Results

Patients’ characteristics, clinical, biochemical, and radiological features at presentation

In total, 383 patients were identified for this study; 256 (256/383; 67% male) with a median follow-up duration of 8 years (IQR 5-10 years). The median age for the cohort was 57 years (IQR 48-67 years).

The leading presenting symptom was visual dysfunction (228/383; 60%). Initial clinical presentation due to hypopituitarism occurred in 58 patients (58/377, 15%). On further endocrine evaluation, 235 patients (235/377; 62%) had evidence of deficiency of at least one pituitary hormone. One third of the patients
had GH deficiency and hypogonadotropic hypogonadism was recorded in 161 patients (161/375; 43%). Dysfunction of hypothalamic-pituitary-adrenal axis was documented in 132 patients (132/375; 36%) while 157 patients (157/375; 42%) had secondary hypothyroidism. Anterior panhypopituitarism was reported in 100 patients (100/377; 26%).

Anterior panhypopituitarism at presentation was more common in men (83/253; 33%) than women (17/124; 14%) (p = 0.001) and observed more with increasing age with a median age of 62 years versus 56 years for those with no preoperative anterior panhypopituitarism (p = 0.005). Furthermore, it was more evident in patients with larger tumours with suprasellar and parasellar extension (41/123; 41%) than intrasellar macroadenoma (59/249; 24%) (p = 0.05). There were no reported cases of central diabetes insipidus on presentation.

Sixty-six patients had pituitary macroadenoma detected incidentally on radiological imaging (66/383; 17%) and secondary to headache in 41 patients (41/383; 11%). Twelve patients (12/377; 3%) were admitted due to pituitary apoplexy.

Treatment

With regards to treatment modality; 318 patients (318/383; 83%) were treated with surgery alone and 65 patients (65/383; 17%) received radiotherapy at some point after surgery. External beam irradiation of 50.4 Gray in 28 daily fractions was delivered to 63 patients while 2 patients were treated with Gamma Knife radiosurgery. Patients treated with surgery and radiotherapy were younger (median age = 53 years) than those treated with surgery alone (median age = 59 years) (p = 0.004). With regards to histological data, 271 patients (371/383; 97%) had gonadotroph adenomas and 12 patients (12/383; 3%) had plurihormonal adenomas, all were clinically and biochemically non-functioning.

Pituitary function after receiving therapy for NFPMs

New onset of hormone deficiency in patients with normal endocrine function at presentation:

The incidence of new individual pituitary hormone deficiency as well as anterior panhypopituitarism was significantly higher among patients received surgery and radiotherapy than those treated with surgery alone (Table 1.). The risk of developing endocrine insufficiency in those received irradiation varied from 3 times in the case of FSH/LH dysfunction to 9 times in central hypothyroidism.

Pituitary hormone recovery after treatment in patients presented with hypopituitarism:

When comparing pituitary function at latest review with baseline levels at presentation for those presented with pituitary dysfunction; pituitary-adrenal axis recovered in 41 patients (41/132; 31%) whereas reversal of growth hormone deficiency occurred in 28 patients (28/115; 24%) (Table 2). Normal gonadal function was observed in 36 patients (36/160; 23%) and secondary hypothyroidism resolved in 20 patients (20/157; 13%). Improvement in anterior panhypopituitarism was reported in 32 patients (32/100; 32%). Across the full cohort, younger age was observed to have a higher rate of improvement in
gonadotropin deficiency (p = 0.004), secondary hypocortisolism (p = 0.01) and anterior
panhypopituitarism (p = 0.006). Gender and evidence of complete resection of NFPMs on postoperative
MRI scan was not related to frequency of pituitary recovery.

The likelihood of improvement in gonadotropins and TSH deficiencies as well as anterior
panhypopituitarism for patients treated with surgery and radiotherapy was significantly less than those
who underwent surgery only. Notably, none of TSH deficient patients regained normal thyroid function
post irradiation.

Hypopituitarism for the full cohort at latest follow up:

In total, 165 patients (165/383; 43%) were GH deficient (Table 3). Secondary hypogonadism was reported
in 178 patients (178/383; 46%) while 156 patients (156/383; 41%) suffered secondary hypercortisolism.
Thyroid dysfunction was recorded in 206 patients (206/383; 54%) and 133 patients (133/383; 34%) had
anterior panhypopituitarism. Twenty-three patients (23/383; 6%) developed permanent cranial diabetes
insipidus. Anterior panhypopituitarism was more commonly observed in men (102/256; 40%) than
women (31/127; 24%) (p = 0.003). Patients who received postoperative pituitary radiotherapy had a
greater degree of partial and complete hypopituitarism than those treated with surgery alone. In addition,
those who underwent surgery alone had higher GH, ACTH and TSH deficiency free survival probability
than those who received surgery and radiotherapy (Figure 1.). Overall, 105 patients (105/383; 27%) had
no evidence of pituitary dysfunction at latest endocrine evaluation.

Discussion

Principal findings

In this study, we describe the extent of preoperative endocrine dysfunction of NFPMs, the impact effect of
surgery and radiotherapy on pituitary function, and the likelihood of hormone deficit recovery during
follow up. We report the following principal findings: (1) hypopituitarism commonly occurs in patients
with NFPMs without relevant clinical symptoms prior to presentation; (2) patients treated with surgery
and radiotherapy had a higher rate of permanent pituitary dysfunction than those that underwent surgery
alone; (3) Recovery of pituitary function was significantly less frequent in patients who received surgery
and radiotherapy (4) Younger patients had a higher degree of endocrine recovery after NFPMs treatment.

Comparison with other studies

Mechanical compression and damage of the adenohypophysis by the enlarging NFPMS can lead to
endocrine dysfunction\textsuperscript{11}. In addition, compression of the pituitary portal circulation due to mass effect
has been speculated to cause hypopituitarism\textsuperscript{12}. A substantial number of our patients had evidence of
pituitary hormone deficiency on laboratory assessment at presentation despite being asymptomatic.
Hypopituitarism often develops insidiously and remains undiagnosed until the patient undergoes full
clinical and endocrine evaluation\textsuperscript{11}. Interestingly in this study, male gender, older age, and NFPMs
extending beyond the sella turcica, were associated with a higher rate of anterior panhypopituitarism at presentation. Jahangiri et al.\textsuperscript{13} reported a correlation between any degree of preoperative hypopituitarism and old age, gender and large pituitary adenomas but not linked to complete hypopituitarism. Zhang et al.\textsuperscript{14} recorded significantly lower preoperative levels of thyroxine, GH, IGF-1, FSH, and LH in patients with giant NFPAs when compared with those having macroadenoma demonstrating the impact of larger NFPAs on pituitary function. Our cohort with reported partial and complete hypopituitarism at diagnosis is in line with other studies in the literature\textsuperscript{8,11,14}. The lower frequency of GH deficiency in this study may not reflect the overall incidence of this condition as GH dynamic tests were only performed for selected cases prior to surgery.

The occurrence of new pituitary dysfunction post therapy can vary according to treatment modality. Postoperatively, the likelihood of developing pituitary dysfunction has been linked to many factors: the operating neurosurgeon, the size of pituitary tumour, the degree of surgical manipulation and the need for multiple surgeries to deal with recurrent disease\textsuperscript{15}. Similarly, the occurrence of new onset pituitary insufficiency post radiotherapy depends on the radiation dose, technique and follow-up duration\textsuperscript{16,17}. It has been estimated that around 30-60\% of patient may develop endocrine dysfunction after pituitary external beam irradiation\textsuperscript{16}. We demonstrated that the combination of surgery and radiotherapy is associated with significantly higher risk of pituitary dysfunction than surgery alone, shorter hormone deficiency free survival and less frequent hormone recovery over the long term. The pathophysiology of radiation induced hypopituitarism is complex and not very well understood. Several mechanisms have been proposed in the literature to elucidate the relation between irradiation and hypothalamic-pituitary dysfunction; this includes thalamic vascular damage with subsequent pituitary atrophy, microstructural change and axonal loss of the hypothalamus, and alterations of hypothalamic neurotransmitters with subsequent endocrine and metabolic disturbance\textsuperscript{18–20}. Recovery of pituitary dysfunction following treatment remains uncertain with no clear predictive clinical and radiological features. In this study younger age patient had increased likelihood of regaining normal endocrine function. Sex and postoperative evidence of residual tumour didn't correlate with overall recovery of pituitary hypofunction. This contrasts the findings of Webb et al.\textsuperscript{21} who reported better improvement in pituitary function in those with no tumour remanent. Of note, Little et al.\textsuperscript{22} did not identify any predictors for regaining normal endocrine function.

In our centre, all patients are discussed in the pituitary multidisciplinary meeting to assess the need for surgery with careful consideration of the use of radiotherapy. We currently use proton beam therapy to treat children, teenagers and young adults, up to their 25th birthday, to reduce the late effects of radiation, according to the NHS commissioning criteria. We routinely perform full basic and dynamic endocrine testing for GH and ACTH axes 6-8 weeks after surgery, and on at least annual regular intervals regular intervals when clinically indicated during follow-up after surgery and radiotherapy.

\textbf{Study strengths and weaknesses}
This study included a large number of patients with NFPMs with a long follow-up duration making the finding generalizable. However, it is amenable to weaknesses of observational research including data selection and loss. Although gonadotropin expressing adenoma are commonly encountered in clinical practice, this study didn't include other subtypes of silent adenomas like non-functioning somatotroph and lactotroph adenomas. One of the important limitations in this study is the lack of data of preoperative tumour size and postsurgical tumour reduction which may be an important influencing factor of hypopituitarism and radiotherapy administration. Those treated with surgery and radiotherapy likely had larger tumours which is a cofounding factor in the incidence of hypopituitarism.

**Conclusion**

Nonfunctioning pituitary macroadenomas are associated with significant degree of hypopituitarism at time of diagnosis as well as after treatment. Both surgery and radiotherapy increase the risk of pituitary dysfunction. Hypopituitarism as a side effect of radiotherapy must be considered when this treatment is offered for tumour control.

Recovery of pituitary hormone deficit may occur post therapy. Patients should have regular endocrine evaluation post treatment to assess improvement in pituitary hypofunction and the need for long term replacement therapy.

**Declarations**

**Conflict of Interest Statement and Author Declaration**

All authors have no conflict of interest and will complete conflict of interest statement.

**Funding Statement**

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**References**


**Tables**

**Table 1**


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<th>Total</th>
<th>Surgery</th>
<th>Surgery and Radiotherapy</th>
<th>P value</th>
<th>Odds ratio</th>
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<tr>
<td>GH</td>
<td>74/260  (28%)</td>
<td>46/217 (21%)</td>
<td>28/43 (65%)</td>
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<td>FSH/LH</td>
<td>48/214  (23%)</td>
<td>33/179 (19%)</td>
<td>15/35 (43%)</td>
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<td>ACTH</td>
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<td>34/203 (17%)</td>
<td>23/40 (58%)</td>
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<td>TSH</td>
<td>64/218  (29%)</td>
<td>41/186 (22%)</td>
<td>23/32 (72%)</td>
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**Table 2**

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<th>Surgery</th>
<th>Surgery and radiotherapy</th>
<th>P value</th>
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<td>GH</td>
<td>28/115 (24%)</td>
<td>27/99 (27%)</td>
<td>1/16 (6%)</td>
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<td>FSH/LH</td>
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<td>0/27 (0%)</td>
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Table 3

Pituitary hormones dysfunction for the full cohort with non-functioning pituitary macroadenomas at latest review. GH: Growth Hormone; FSH: Follicle Stimulating Hormone; LH: Luteinising Hormone; ACTH: Adrenocorticotropic Hormone; TSH: Thyrotroph Stimulating Hormone.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Surgery</th>
<th>Surgery and radiotherapy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH</td>
<td>165/383 (43%)</td>
<td>118/318 (37%)</td>
<td>47/65 (72%)</td>
<td>&lt;0.0001</td>
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<td>FSH/LH</td>
<td>178/383 (46%)</td>
<td>136/318 (43%)</td>
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<td>43/65 (62%)</td>
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Figures

Figure 1
