Relapse of pituitary adenomas after surgery

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7-10 November 2013, 6th Joint Meeting with AACE
American Association of Clinical Endocrinologists
**Cushing’s Disease**

- This man has loss of secondary sexual characteristics and absence of pubic hair.
- Hypopit patients may have fine wrinkling of skin esp. around eyes and mouth and look pale.
- The patient may complain of feeling cold, lethargic, dizzy on standing, constipation, weakness.

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**Acromegaly**

- Spontaneous discharge from one nipple only.
- Benign growth in single milk duct.

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**Galactorrhoea**

- Two images of a man and a woman showing acromegaly.
Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK)

Alberto Fernandez, Niki Karavitaki and John A. H. Wass

Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK
81,449 inhabitants
91% of study population

<table>
<thead>
<tr>
<th></th>
<th>PRL</th>
<th>NFA</th>
<th>ACRO</th>
<th>CD</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>37</td>
<td>18</td>
<td>7</td>
<td>1</td>
<td>64</td>
</tr>
<tr>
<td>Prevalence</td>
<td>45.6</td>
<td>22.2</td>
<td>8.6</td>
<td>1.2</td>
<td>78.8</td>
</tr>
<tr>
<td>(1,000,000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Duration of symptoms (yrs)</td>
<td>0.5-12</td>
<td>0-8</td>
<td>1.5-15</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Approximately 1 per 1,000 clinically significant pituitary adenomas
Distribution of pituitary adenomas subtypes

- NFA: 28%
- ACRO: 11%
- CD: 2%
- UFS: 2%
- PRLoma: 57%
Prolactinoma

Treatment of choice cabergoline 0.25 – 3mg per week

No cardiac valve effects
Valvular heart disease and the use of cabergoline for the treatment of prolactinoma

Neil Herring*, Cezary Szmigielski*, Harald Becher*, Niki Karavitaki† and John A. H. Wasst†

*Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford University and †Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK
Conclusions

We found no evidence of increased mitral valve tenting area/height, valvular thickening or significant regurgitation with the long term administration of the commonly used doses of cabergoline to treat prolactinoma.
Recurrence of hyperprolactinaemia following discontinuation of dopamine agonist therapy in patients with prolactinoma occurs commonly especially in macroprolactinoma

Thomas M. Barber*, Julia Kenkre*, Catherine Garnett*, Rebecca V. Scott*, James V. Byrne† and John A. H. Wass*

*Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, and †Department of Radiology, Churchill Hospital, Oxford OX3 7LJ, UK
Do Macroprolactinomas Recur after 3-5 Years Treatment?

Number of patients: 15
Treated > 3 years (mean 7.5 years)
Prolactin suppressed to normal
Do Macroprolactinomas Recur after 3-5 Years Treatment?

Recurrence of hyperprolactinaemia in 14 (93%)
Mean time to recurrence 8.8 months
Mean prolactin at baseline 28,246 mU/L
on treatment 144 mU/L
at recurrence 2,236
(411-12,847)
Do Macroprolactinomas Recur after 3-5 Years Treatment?

Most macroprolactinomas have a recurrence of hyperprolactinaemia.
Does hypopituitarism recover when macroprolactinomas are treated with cabergoline?

Niki Karavitaki*, Ruxandra Dobrescu*, James V. Byrne†, Ashley B. Grossman* and John A. H. Wass*

*Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital and †Department of Neuroradiology, John Radcliffe Hospital, Oxford, UK
Do patients with macroprolactinoma have an improvement in pituitary function?

11 Patients (10 M 1 F) aged mean 38 (17-56)

9 Followed for 3 years; 2 for 2 years

All achieved normal prolactin

All had significant tumour shrinkage

All had pituitary function assessed yearly

(insulin/glucagon test and basal bloods)
Hormone deficits

- GH (n=11)
- LH/FSH (n=10)
- ACTH (n=11)
- TSH (n=10)

%
Trans-sphenoidal Surgery for Microprolactinoma: an acceptable alternative to dopamine agonists?

Turner et al. 1999, 140, 43-47

Microprolactinoma 32 female patients

Intolerant 31% Resistant 9% Intolerant & Resistant 12.5%
Trans-sphenoidal surgery for microprolactinoma: an acceptable alternative to dopamine agonists?

*Turner et al., 1999, 140, 43-47*

25 (79%) cured (normal post op prolactin)

Follow up 6 years (2 months to 16 years)

1 (4%) recurrence @ 12 years

28.6% GH deficient

8.0% diabetes insipidus
Macroprolactinoma

Pre-treatment
Prolactin (off drugs)
MRI
Anterior pituitary function
Visual fields

Warn about CSF rhinorrhea

Start cabergoline 0.5 mg weekly/
0.5 mg increments weekly or more rapidly if field defects

Measure prolactin at each increment
Fields at one month
Scan at 3 months
8% resistant 5% intolerant
1) Other dopamine agonist 2) Radiotherapy 3) Surgery

Stop therapy at 5 years if prolactin normal
MRI small tumour not touching chiasm
Nonsurgical Cerebrospinal Fluid Rhinorrhea in Invasive Macroprolactinoma: Incidence, Radiological, and Clinicopathological Features

S. G. I. Suliman,* A. Gurlek,* J. V. Byrne, N. Sullivan, G. Thanabalasingham, S. Cudlip, O. Ansorge, and J. A. H. Wass
Non Surgical CSF Rhinorrhoea

114 patients
macroprolactinoma
Incidence of CSF rhinorrhoea
Factors predicting leakage
Makers of invasiveness
Non Surgical CSF Rhinorrhoea

8.7%

2.6% 6.1%

spontaneous  d.a induced

Male preponderance 9.1% (p 0.008)
Dopamine agonist resistance higher in csf rhinorrhoea 30% vs. 5% (p 0.003)

Not related to baseline prolactin level, rate of prolactin decline, tumour volume at diagnosis
What is the natural history of nonoperated nonfunctioning pituitary adenomas?

N. Karavitaki*, K. Collison*, J. Halliday*, J. V. Byrne†, P. Price‡, S. Cudlip§ and J. A. H. Wass*

*Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK,
†Department of Neuroradiology, John Radcliffe Hospital, Oxford, UK, ‡Department of Diabetology and Endocrinology, The Great Western Hospital, Swindon, UK and §Department of Neurosurgery, John Radcliffe Hospital, Oxford, UK
Series of patients systematically assessing the outcome of NFAs not treated by surgery or radiotherapy during long follow-up periods are limited.

Aim: investigate the outcome of a series of consecutive patients with presumed NFA (micro- or macroadenoma) not offered treatment at initial presentation (for a number of reasons) and to identify possible factors predicting subsequent increase in the tumour size.
<table>
<thead>
<tr>
<th></th>
<th>Total tumours</th>
<th>Microadenomas</th>
<th>Macroadenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean follow-up, months (range)</strong></td>
<td>42 (8–128)</td>
<td>41 (8–128)</td>
<td>43 (9–98)</td>
</tr>
<tr>
<td><strong>Increase in size, n (%)</strong></td>
<td>14/40 (35)</td>
<td>2/16 (12.5)</td>
<td>12/24 (50)</td>
</tr>
<tr>
<td><strong>Mean time of detection, months (range)</strong></td>
<td>34.3 (11–98)</td>
<td>21 (20–22)</td>
<td>36.5 (11–98)</td>
</tr>
<tr>
<td>Stable, n (%)</td>
<td>21/40 (52.5)</td>
<td>13/16 (81.3)</td>
<td>8/24 (33.3)</td>
</tr>
<tr>
<td>Decrease in size, n (%)</td>
<td>5/40 (12.5)</td>
<td>1/16 (6.3)</td>
<td>4/24 (16.7)</td>
</tr>
<tr>
<td>Mean time of detection, months (range)</td>
<td>24.6 (7–46)</td>
<td>19 (–)</td>
<td>26 (7–46)</td>
</tr>
</tbody>
</table>
Fig. 2  Probability of tumour enlargement in patients with microadenoma during the follow-up period.

Fig. 3  Probability of tumour enlargement in patients with macroadenoma during the follow-up period.
Do the limits of serum prolactin in disconnection hyperprolactinaemia need re-definition? A study of 226 patients with histologically verified non-functioning pituitary macroadenoma

Niki Karavitaki* Gaya Thanabalasingham* Helena C. A. Shore* Raluca Trifanescu* Olaf Ansorge† Niki Meston‡ Helen E. Turner* and John A. H. Wass*

*Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, †Neuropathology Department, Radcliffe Infirmary and ‡Department of Chemical Pathology, John Radcliffe Hospital, Oxford, UK
Disconnection Hyperprolactinaemia

<table>
<thead>
<tr>
<th></th>
<th>Median prolactin</th>
<th></th>
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<tbody>
<tr>
<td>All</td>
<td>386 mU/L (16-3257)</td>
<td></td>
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<tr>
<td>No drugs</td>
<td>363 mU/L (16-2565)</td>
<td></td>
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</tbody>
</table>

Serum prolactin < 2000 mU/L

98.7% (all)
99.5% (no drugs)
Serum PRL in patients not on PRL increasing drugs

99.5% (n = 184)

0.5% (n = 1)

Grids:
- □ 2000–3000 mU/l
- □ < 2000 mU/l
Can we ever stop imaging in surgically treated and radiotherapy-naive patients with non-functioning pituitary adenoma?

Raghava Reddy, Simon Cudlip\textsuperscript{1}, James V Byrne\textsuperscript{2}, Niki Karavitaki and John A H Wass

Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, University of Oxford, Oxford OX3 7LJ, UK, Departments of \textsuperscript{1}Neurosurgery and \textsuperscript{2}Neuroradiology, The John Radcliffe Hospital, Oxford, UK

(\textit{Correspondence should be addressed to J A H Wass; Email: john.wass@noc.nhs.uk})
Table 2: Re-growth rates detected by 1, 5 and 10 years in the 3 groups based on postoperative imaging details.

<table>
<thead>
<tr>
<th></th>
<th>No residual tumour (A)</th>
<th>Intracellular residual (B)</th>
<th>Extrasellar residual (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At 1 year</strong></td>
<td>0%</td>
<td>1.5%</td>
<td>4.2%</td>
</tr>
<tr>
<td><strong>At 5 years</strong></td>
<td>0%</td>
<td>20%</td>
<td>53%</td>
</tr>
<tr>
<td><strong>At 10 years</strong></td>
<td>6%</td>
<td>53%</td>
<td>80%</td>
</tr>
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**P Value**

<table>
<thead>
<tr>
<th></th>
<th>Vs A</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>-</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
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</table>
Figure 1: Relapse rate according to postoperative scan classification.
Potential new treatments of non-functioning pituitary adenomas

Dopamine agonists
Somatostatin analogues
Fig. 2 Success and failure rates with time of surgery. ■ Remission; □ Failure.

Control of growth hormone and IGF1 in patients with acromegaly in the UK: responses to medical treatment with somatostatin analogues and dopamine agonists

Trevor A. Howlett, Debbie Willis, Gillian Walker, John A.H. Wass, Peter J. Trainer and the UK Acromegaly Register Study Group (UKAR-3)*

UK Acromegaly Register, Society for Endocrinology, Bristol, UK
GH levels and GH and IGF1 control in individual patients at latest value on and off medical treatment, stratified by the last era of observations

Howlett et al, Clinical End. 2013

<table>
<thead>
<tr>
<th>last era of observation</th>
<th>1990s</th>
<th>2000s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of last GH value - on RX</td>
<td>15.1</td>
<td>12.5</td>
</tr>
<tr>
<td>Latest values whether On or Off GH controlled</td>
<td>38%</td>
<td>56%</td>
</tr>
</tbody>
</table>
Responses of GH and IGF1 to treatment with somatostatin analogues (SMS) and dopamine agonists (DA) in treatment courses during the 2000s
Control of GH and IGF1 by dopamine agonists (DA) and somatostatin analogues (SMS) in 2000s, stratified by the precourse GH.
Comparison of biochemical control of acromegaly in different UK centres and number of cases in each centre
# Pituitary Surgery Results - Oxford

<table>
<thead>
<tr>
<th></th>
<th>Acromegaly</th>
<th>Prolactinoma</th>
<th>Cushing’s</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cure rate</strong></td>
<td>90-100%</td>
<td>79%</td>
<td>63%</td>
</tr>
<tr>
<td>(microadenoma)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recurrence rate</strong></td>
<td>5.7% @ 4.4 yr.</td>
<td>4.0% @ 5.0 yr.</td>
<td>11.5% @ 3.3 yr.</td>
</tr>
<tr>
<td><strong>TSH deficiency</strong></td>
<td>5.0%</td>
<td>0%</td>
<td>25.8%</td>
</tr>
<tr>
<td>(Post-op)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Medical treatment of resistant acromegaly.

SOM230 (Pasireotide) improves growth hormone and IGF1 outcome.
Monitoring

Annual monitoring of

- GH - g.t.t.<1, basal <1.8ng/L
- IGF$_1$ - normal

+/- MRI pituitary

Cardiovascular

- blood pressure
- echo

Carbohydrate metabolism

Rheumatology

Colonoscopy/mammography/PSA
New drugs for acromegaly

Oral octreotide
SOM 230 (pasireotide)
GH secretion inhibitors
Causes of Cushing’s syndrome

- Pseudo-Cushing’s syndrome:
  - Alcoholism <1%
  - Severe depression 1%
- ACTH-dependent:
  - Pituitary adenoma 68% (Cushing’s disease)
  - Ectopic ACTH syndrome 12%
  - Ectopic CRH secretion < 1%
- ACTH independent:
  - Adrenal adenoma 10%
  - Adrenal carcinoma 8%
  - Nodular (macro or micro) hyperplasia 1%
  - Carney complex
- Exogenous steroids including skin creams e.g., clobetasol
Undetectable postoperative cortisol does not always predict long-term remission in Cushing's disease: a single centre audit.


Retrospective analysis of 97 patients:
followed for a mean of 92 months (six months to 29 years)

Remission rate with an undetectable cortisol 68.5%

11.5% recurrence at 36 months

Van de Pas et al, Clin End. 2013; 78:481-8

10 x increased risk of thromboembolism in Cushing’s

Increased production of pro-coagulant factors
Impaired fibrinolytic activity

? Thromboprophylaxis after surgery
A 12 Month Phase 2 Study of Pasireotide in Cushing’s disease
Colao et al, NEJM 2012: 366; 914-24

Double blind study 162 patients with Cushing’s disease

Subcutaneous pasireotide – 600mcg
800mcg

Aim normal urinary cortisol
A 12 Month Phase 2 Study of Pasireotide in Cushing’s disease
Colao et al, NEJM 2012: 366; 914-24

12 out of 82 600 mcg
21 out of 80 900 mcg

Achieved a normal urinary cortisol
A 12 Month Phase 2 Study of Pasireotide in Cushing’s disease
Colao et al, NEJM 2012: 366; 914-24

Hyperglycaemic events 118 out of 162
CLINICAL STUDY

Mortality in Cushing’s syndrome: systematic analysis of a large series with prolonged follow-up

G Ntali, A Asimakopoulou¹, T Siamatras, J Komninos, D Vassiliadi¹, M Tzanela¹, S Tsagarakis¹, A B Grossman, J A H Wass and N Karavitaki

Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ, UK and ¹Department of Endocrinology, ‘Evangelismos’ General Hospital, Athens, Greece

(Correspondence should be addressed to N Karavitaki; Email: niki.karavitaki@ouh.nhs.uk)
Long term survival and cause of death in Cushing’s syndrome

Two large tertiary centres

Variables predicting mortality

480 subjects

- 311 Cushing’s disease
- 74 adrenal Cushing’s disease
- 33 Ectopic ACTH

Cushing’s disease

- Ten year survival 95.3%
- 71% of deaths due to cardiovascular disease or sepsis
Mortality in Cushing’s syndrome: systematic analysis of a large series with prolonged follow-up
Ntali et al, EJE, 2013; 169: 715-723

SMRs high 9.3 (95% confidence intervals 6.2-13.4)

Ectopic ACTH 77.6% five years survival

Mortality effected even after successful cure
Pituitary apoplexy in non-functioning pituitary adenomas: long term follow up is important because of significant numbers of tumour recurrences

A. Pal*, C. Capatina*, A.P. Tenreiro*, P.D. Guardiola*, J.V. Byrnet†, S. Cudlip‡, N. Karavitaki* and J.A.H. Wass*

*Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, University of Oxford; †Department of Neuroradiology, The John Radcliffe Hospital, Oxford; ‡Department of Neurosurgery, John Radcliffe Hospital, Oxford, UK

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NFA recurrence rates after classical pituitary apoplexy

32 patients mean age 58.5 years (29-85)
mean follow up 65 months (3-211)
5 given adjuvant radiotherapy

3 (11.1%) patients relapsed at a mean 51 months
Relapse Free Survival After Classical Pituitary Apoplexy (NFAs)
FUTURE TREATMENTS OF PITUITARY TUMOURS

1. Genesis of pituitary tumours: PTTG, Angiogenesis, AIP gene
2. Replacement therapy: DHEA?
3. Surgery: Fewer expert centres, endoscopy
4. Drugs: selective Somatostatin receptor antagonists, Pegvisomant and oral octreotide
5. Radiotherapy: Gamma knife
6. Pituitary tumour gene therapy