Surgical and Non-Surgical Approaches for Large Pituitary Masses

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Large Adenomas: Definitions, Epidemiology, and Clinical Presentations

- Pituitary adenomas have long been classified as microadenomas (less than 10 mm in diameter) versus macroadenomas (10 mm or larger in diameter).
- Recognition that outcomes can be worse for the 6-17% of adenomas that are particularly large has led some to further define:
  1. Large adenomas (30 mm or larger)
  2. Giant adenomas (40 mm or larger)

Introduction

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Clinical presentation of large adenomas

- Hormone secretion - 55% of large adenomas are non-functional adenomas (NFAs).
- Age/gender breakdown – same as non-large adenomas (UCSF – non-large: 57 years, 65% male; large: 53 years, 68% male).
- Symptoms - headache in adenoma patients does not become more common with increasing size (unlike vision loss and hypopituitarism)

Endocrine consequences of large adenomas

Nearly 25% of patients with giant NFAs will have symptomatic hypopituitarism, of which the vast majority have hypogonadism.

Laboratory deficits include:

<table>
<thead>
<tr>
<th>Hormone deficient</th>
<th>% of patients</th>
<th>% of total</th>
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<tbody>
<tr>
<td>GH</td>
<td>28</td>
<td>100</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>28</td>
<td>95</td>
</tr>
<tr>
<td>TSH</td>
<td>15</td>
<td>61</td>
</tr>
<tr>
<td>ACTH</td>
<td>19</td>
<td>67</td>
</tr>
<tr>
<td>PRL</td>
<td>5</td>
<td>25</td>
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Source: JCEM 62: 1173, 1986
Surgical Management of Large Adenomas

Microscopy vs. Endoscopy – UCSF results re: NFA size inflection point

- No difference in GTR rates was noted between the approaches
- Correlating GTR rates with size revealed the SI dimension to be where an inflection point occurred.
- This inflection point was smaller with the microscopic approach (3.1 cm – GTR rate if SI<3.1 cm=65%, GTR rate if SI≥3.1 cm=32%) than with endoscopic cases (4.0 cm – GTR rate if SI<4.0 cm =59%, GTR rate if SI≥4.0 cm=28%)

Transcranial Approaches for Large Adenomas

Transcranial approaches needed for giant adenomas that violate arachnoid planes and leave tumor in locations difficult to access endonasally (sylvian fissure, corpus callosum, third ventricle)

1. Interhemispheric
2. Subfrontal (uni- or bilateral)
3. Pterional +/- orbital bar removal

Crani for pituitary tumors – anatomic considerations influencing approach

10% chiasm over tuberculum–prefixed
80% chiasm over diaphragm
10% chiasm over dorsum–postfixed

Two implications of the anatomy on pituitary adenomas – (1) affects the type of visual field defect (contralateral HH, bitemporal HH, and monocular deficit); (2) influences choice of craniotomy (avoid subfrontal for prefixed chiasm)

Rate of GTR and approach selection for macro/large/giant adenomas

UCSF experience – 721 adenomas 2007-2012
1. Macroadenomas (10-29 mm diameter) – 411 cases (57%), all resected endonasally, 85% GTR
2. Large adenomas (30 mm or larger) – 79 cases (11%), all resected endonasally, 75% GTR
3. Giant adenomas (40 mm or larger) – 50 cases (7%): 40 endonasal resections, 8 staged endonasal/craniotomy approaches, and 2 pure craniotomies. Of craniotomies: 5 orbitozygomatic, 3 subfrontal, 2 interhemispheric. 44% GTR

Postoperative results and adjuvant therapy for large nonfunctional adenomas
Case – staged transsphenoidal and transcranial approaches

33 year old male with 3 years of right eye blindness that he was told was “optic atrophy” presents with headache.

Interhemispheric Transcranial

62 year old female with over 15 years of right eye blindness and temporal field cuts in left eye, presents with headache. Labs reveal hypopituitarism.

Orbitozygomatic Transcranial

Case – staged transsphenoidal and transcranial approaches

Giant adenoma seen through a transsylvian approach

Frontal Temporal

Giant adenoma recurrence – UCSF experience

- 31 giant adenomas compared to 66 non-giant adenomas.
- Rate of complete resection – 80% (non-giant) vs. 55% (giant) (p=NS).
- No completely resected adenomas recurred during short follow-up, while progression rates for subtotally resected adenomas did not differ in giant vs non-giant.

Radiation for large pituitary adenomas

While no randomized trial has investigated postoperative radiation for giant NFAs, several retrospective series have shown benefit. The size of the targets in subtotally resected large or giant adenomas sometimes requires radiation therapy rather than radiosurgery.

Postoperative endocrine improvement in large NFA patients

Reported rates of recovery - 15% (GH), 30% (testosterone), 40% (adrenal), and 50-60% (thyroid).

Serum TSH responses to TRH

Mean cortisol

Mean glucose

Source: JCEM 62, 1986

Source: Neurosurgery 60: 993, 2007
Endocrine recovery after surgery for large NFAs (UCSF series)

- UCSF experience – Of 129 giant/large adenomas over 5 years, 125 had documented hypopituitarism preoperatively.
- Rates of correction 6 weeks after surgery without hormone replacement were 20% for testosterone, 36% for thyroid, and 29% for cortisol.
- No patients with preoperative TSH below 0.03 units, testosterone below 2.0 units, or cortisol below 1 µg/dL was able to be corrected sufficiently with surgery to avoid hormone replacement.

Etiology of Large Adenomas

Three possible etiologies of giant adenomas

- i. start out with different biology than smaller adenomas
- ii. result from longer incubation periods
- iii. result from a second hit in a smaller adenoma

i. Different biology? - MIB-1 labeling in large vs. non-large adenomas

The UCSF experience 2005-2008

MIB-1 labeling

<table>
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<tr>
<th>Size of Adenoma</th>
<th>MIB-1 Labeling</th>
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<tr>
<td>&lt; 30 mm</td>
<td>0.0%</td>
</tr>
<tr>
<td>30 mm or larger</td>
<td>3.0%</td>
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i. Different biology? - Atypical Adenomas

- In 2004, WHO revised classification of pituitary adenomas included an “atypical” variant with
  1. MIB-1>3%
  2. excessive p53 immunoreactivity
  3. increased mitoses.
- In our UCSF series, atypical adenomas were more invasive but not larger. We also found atypical adenomas to recur more frequently, but conversion from non-atypical to atypical did not occur.

i. Different biology? – p53 polymorphism

- Performed full sequencing of the p53 gene in 35 pituitary adenomas
- Polymorphism rs1042522:C>G in codon 72 of exon 4 whose C variant produces a proline and occurs in 64% of the population, has a G variant producing an arginine in 62% of adenomas (p=1.09x10^-8).
- The G variant renders adenomas more proliferative and causes patients to present a decade earlier with symptoms.
Given lack of proliferative differences could longer adenomas just arise from prolonged incubation (i.e. delay in diagnosis?)

In the UCSF series, the greatest delay in being diagnosed with adenoma in patients with visual symptoms occurred in elderly non-white patients who had a delay from onset of visual symptoms to adenoma diagnosis of over 6 months compared to 2 months in younger white patients). Delayed diagnosis in patients with visual symptoms often due to not seeking care or being diagnosed with other conditions (cataracts, retinopathy, glaucoma), leading to a greater incidence of presenting with large adenomas.

Unfortunately elderly patients with prolonged duration of visual symptoms are unlikely to return to baseline vision after surgery, particularly when elderly.

Investigational drugs for large pituitary adenomas

1. Protein kinase C inhibitors
   PKC activity increased in adenomas; hypericin (PKC inhibitor) inhibits proliferation of adenoma cell lines

Investigational agents studied pre-clinically for large adenomas

ii. Socioeconomic factors leading to delayed diagnosis

ii. Longer incubation period? - Factors leading to delayed diagnosis

iii. A second hit? – Ongoing studies

Site-directed biopsies have uncovered the regional heterogeneity of malignant tumors
Preliminary work has suggested similar genetic heterogeneity in pituitary adenomas

Investigational drugs for large pituitary adenomas

2. Targeting Rb inactivation
   • Rb (retinoblastoma) pathway alterations seen in 75-90% of adenomas. Aberrantly activated Rb/E2F1 pathway releases E2F1 to induce PTTG1 (pituitary tumor transforming gene), resulting in chromosome instability and proliferation.
   • Doxorubicin targets Rb-deficient cells (preclinical)
   • CDK2 inhibitor R-roscovit for Rb-hyperphosphorylated adenomas (clinical trial ongoing)
Investigational drugs for large pituitary adenomas

3. Folate-targeted therapy

Folate receptor α uniquely overexpressed in pituitary adenomas relative to normal gland

This could enable treatment of giant adenomas with folate-drug conjugate or folate-based radionuclide therapy

Conclusions

1. Large non-functional pituitary adenomas can be radiographically controlled with aggressive (sometimes staged) surgical resections and radiation therapy.

2. Size does not always reflect aggressiveness and can sometimes reflect incubation period/delay in diagnosis.

3. Continued studies of the molecular etiology of adenomas could give rise to targeted therapies.

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