Nonfunctional Pituitary Adenomas

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Disclosures

None
Overview

1. Introduction to Nonfunctional Pituitary Adenomas
2. Visual Outcomes after Nonfunctional Adenoma Surgery
3. Endocrine Outcomes after Nonfunctional Adenoma Surgery
4. Headache Outcomes after Nonfunctional Adenoma Surgery
5. Recurrence after Nonfunctional Adenoma Surgery
Nonfunctional Pituitary Adenomas – Pathologic Subtypes

• Definition – Pituitary adenoma that does not produce any excessive hormone into the blood

• Pathologic Subtypes –

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null-cell adenoma</td>
<td>9 (25.7)</td>
</tr>
<tr>
<td>Gonadotropin adenoma</td>
<td>16 (45.7)</td>
</tr>
<tr>
<td>Silent ACTH adenoma</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Silent TSH adenoma</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Silent somatotroph adenoma</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Plurihormonal adenoma</td>
<td>2 (5.7)</td>
</tr>
</tbody>
</table>

TSH: Thyroid stimulating hormone, ACTH: Adrenocorticotropic hormone, GnRH/P: Giant nonfunctioning pituitary adenomas

Nonfunctional Pituitary Adenomas – Silent Corticotrophic Adenomas

• Nonfunctional Adenomas that Stain for ACTH

SCA Type I | SCA Type II

Source: Neurosurgery 72:8, 2013
• Higher recurrence rate with Type I SCAs

Pituitary Adenomas – Classification by Size

• 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)
Old classification no longer used - 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.

- This classification stopped being used with the WHO 2016 criteria.

Source: Journal of Neurosurgery 128: 1058, 2018

What do you with an asymptomatic nonfunctional adenoma?

- 42 asymptomatic incidentalomas followed for 1 to 14 years. Mean initial tumor size 18 mm. In 21 patients, the tumor increased by at least 10%, with the increase occurring 8 to 58 months after diagnosis.

- Symptoms were noted in 10 patients during follow up – 4 of these had pituitary apoplexy. Twelve patients went to surgery – 10 with symptoms and 2 with asymptomatic enlargement. Symptoms only developed in tumors whose initial size was > 15 mm

Source: J Neurosurgery 104: 884, 2006
What do you with an asymptomatic nonfunctional adenoma?

Changes in incidentoloma size in 236 patients followed over 2.3 to 8 years in 9 published series 1990-2006

<table>
<thead>
<tr>
<th></th>
<th>↑ SIZE</th>
<th>↓ SIZE</th>
<th>NO CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>19% MICROADENOMAS</td>
<td>10%</td>
<td>6%</td>
<td>84%</td>
</tr>
<tr>
<td>42% MACROADENOMAS</td>
<td>20%</td>
<td>11%</td>
<td>69%</td>
</tr>
<tr>
<td>39% RATHKE’S CYST</td>
<td>5%</td>
<td>16%</td>
<td>78%</td>
</tr>
</tbody>
</table>


Main symptoms of pituitary tumors

1. **Vision loss** – mass effect on the overlying optic chiasm
2. **Hypopituitarism** – mass effect on the surrounding pituitary gland
3. **Headache** – from mass effect on the dura

Example - how a pituitary adenoma could cause symptoms
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### Visual symptoms by pituitary pathology

Frequency of visual symptoms by pathology at UCSF

- **Endocrine-active adenomas**
- **Endocrine-inactive adenomas**
- **Rathke’s cleft cyst**
- **Cranio-pharyngioma**
- **Other**
### Visual symptoms caused by pituitary tumors based on patient anatomy (theory)

<table>
<thead>
<tr>
<th>1. Chiasm over tuberculum (prefixed)</th>
<th>2. Chiasm over diaphragm</th>
<th>3. Chiasm over dorsum (postfixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor visual symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral hemianopsia</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Bitemporal hemianopsia</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Monocular deficit</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>

### Visual symptoms caused by pituitary tumors (reality)

- From January 2003 to July 2012, 967 nonfunctional adenomas resected at UCSF
- 492 (51%) presented with visual symptoms
- Median duration of vision loss prior to surgery was **6.5 months**

#### Visual deficits observed in UCSF adenoma patient cohort (n=967)

<table>
<thead>
<tr>
<th>Deficit</th>
<th>Share of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitemporal hemianopsia</td>
<td>49%</td>
</tr>
<tr>
<td>Monocular</td>
<td>31%</td>
</tr>
<tr>
<td>Quadrantopia in one eye combined with quadrantopia or hemianopia in the other eye</td>
<td>20%</td>
</tr>
</tbody>
</table>
Example of monocular deficit from nonfunctional adenoma

- 48 year old male on coumadin for pacemaker
- status post transsphenoidal resection of nonfunctional adenoma at outside hospital
- referred to us for radiosurgery for residual tumor in left cavernous sinus.
- reoperation due to persistent left eye monocular deficit.

Rectifying monocular deficits can require slightly more lateral exposure
Vision Improvement after Surgery for nonfunctional adenomas

Analysis of postoperative visual improvement after surgery for nonfunctional adenoma patients with preop visual deficits at UCSF 2007-2012:

- 77% had some postoperative improvement in vision
- 37% had postoperative return to baseline vision
- Multivariate analysis revealed increased age and increased duration of visual symptoms before surgery to decrease chance of return to baseline vision after surgery.

Source: Journal of Neurosurgery 116: 283, 2011

Delay in Diagnosing Nonfunctional Adenomas Lowers Chance of Surgery Correcting Vision

- Elderly patients tend to have a greater delay from onset of visual symptoms to adenoma diagnosis (over 6 months compared to 2 months in younger patients).
- Elderly patients often due to not seeking care or being diagnosed with other conditions (cataracts, retinopathy, glaucoma).
- Unfortunately elderly patients with prolonged duration of visual symptoms are unlikely to return to baseline vision after surgery.

Source: JNS 116: 283, 2011
Race and age both increase duration of visual symptoms, reducing postop improvement

![Diagram showing duration of visual symptoms by age/race group]

Source: Journal of Neurosurgery 116: 283, 2011

Apoplexy has less postop visual improvement and associated socioeconomic risk factors

- The extreme form of vision loss in adenoma patients is apoplexy.
- Apoplexy lowers chances of postoperative visual improvement (81% in non-apoplexy cases, 53% in apoplexy cases at UCSF 2003-2012).
- Apoplexy patients were more likely to lack insurance and primary care and in retrospect had symptoms that could have led to the diagnosis of adenoma before apoplexy if they had access to care.

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Hypopituitarism assessment and confirmation of central (pituitary) source

Need to confirm deficiency in downstream hormone and the pituitary hormone to confirm that the deficiency is central (pituitary) rather than at the level of the downstream gland (thyroid, adrenal, etc.)
Predicting incidence of deficits by axis based on anatomy/susceptibility

Some theorize that differential robustness of cells in the normal pituitary gland leads to a growing adenoma causing endocrine deficits in the following sequence: (1) growth hormone, (2) LH/FSH, (3) thyroid, and (4) cortisol.

Nature Reviews Cancer 4: 285, 2004

Hypopituitarism by Axis – Real Incidences

• Rates of preoperative central hormonal deficits at UCSF 2007-2012 for 1015 cases, 305 nonfunctional adenomas. Every patient had some endocrine evaluation but some patients had incomplete evaluations:

• Comparison to Nomikos et al. (Acta Neurochir 146:27, 2004): 721 nonfunctional adenomas with full preop lab panels – 35% adrenocortical, 77% gonadal, 19% thyroid.
Variables associated with Preoperative Pituitary Deficits

- Patients with preoperative endocrine deficit(s) were
  - older (mean age=60 vs. 54 years; P=0.004)
  - More male (64% male vs. 36% female; P=0.0005),
  - Had larger NFAs (mean diameter=2.4 cm vs. 2.1 cm; P=0.02)

- Effect of size on specific axes: size correlated with male/female hypogonadism but not with low thyroid, GH/IGF-1, or cortisol.

Improvement/Normalization of Endocrine Deficits after Nonfunctional Adenoma Surgery

- Difference between nonfunctional adenomas vs. other sellar tumors: delayed improvement unique to nonfunctional adenomas

New Endocrine Deficits after Surgery by axis

- No variables predicted development of new deficits
- Comparison to largest previous study (Webb et al.; *JCEM* 84: 3696, 1999): 56 NFAs – 25% new hypoadrenalism, 16% new reproductive, 14% new GH, 10% new TSH


Threshold for Surgical Correction of Pituitary Deficits

- **TSH**: No correction if < 0.03 mIU/mL (normal=0.45-4.12)
- **Testosterone**: No correction if < 2.0 ng/dL (normal =250-1100)
- **Cortisol**: No correction if < 1 µg/dL (normal=4-22)
- **IGF-1**: No correction if < 25 µg/dL (normal =34-246)
Multivariate Analysis – Factors Predicting Endocrine Improvement after NFA surgery

- Male reproductive and thyroid axes were the two axes most commonly impaired and most likely to get better.
- For these 2 axes, younger age and less severe deficit predicted normalization (P<0.05)

- No variables predicted normalization in other axes:
  - Female Reproductive Axis
  - Cortisol
  - IGF-1

Preoperative and postoperative gland volume

- Measurements of normal pituitary gland volume reveal that most patients experience postoperative expansion of gland

• Patients who do not exhibit postoperative endocrine improvement exhibit lower preoperative gland volume than those who go onto exhibit endocrine improvement (P<0.01).

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Headaches

• Preoperative presentation with headache at UCSF 2007-2012:

![Bar chart showing headache presentation]

Rates of headaches as a complaint versus sole complaint per pathology

![Bar chart showing preoperative headache rates by pathology]
Multivariate Analysis - factors associated with headache in pituitary tumor patients

- Factors associated with headache as a complaint
  - Diagnosis (P=0.01)
    - Most commonly with Rathke’s Cleft Cysts
    - Endocrine-inactive adenomas least common
  - Younger Age (P=0.001)
  - Female Gender (P=0.002)
  - Recurrent Lesions (P=0.04)
- Factors not associated with headache as a complaint
  - Lesion size
  - Suprasellar extension
  - Hypopituitarism

Source: Clin Neurol Neurosurg 132: 16, 2015

Headache in pituitary adenoma patients

- Headache in adenoma patients does not become more common with increasing size (unlike vision loss and hypopituitarism)

Source: Clin Neurol Neurosurg 132: 16, 2015
Rates of headache improvement after pituitary surgery for all patients with headache

- High independent incidences of headaches and pituitary tumors in the general population means that failure of headache to improve postop could mean failure to resolve mass effect or headache unrelated to tumor.
- For all pathologies combined at UCSF 2007-2012, headache improvement recorded at 6 weeks and 6 months postop.

Multivariate Analysis for Headache Improvement

- Factors associated with improvement
  - Gross total resection (GTR) $P=0.04$
  - Younger Age $P=0.03$

- Factors not associated with improvement
  - Duration & location of HA
  - Gender
  - Pathology
  - Lesion size

Source: Clin Neurol Neurosurg 132: 16, 2015
Mechanism of Headache from Pituitary Tumors – is it sellar pressure?

Two patients with suprasellar Rathke’s cleft cysts and headache

Headache better postop

Headache not better postop

A bolt (ICP monitor) placed into the dura can be used to measure intrasellar pressure, which is elevated in patients with headache

Measuring sellar pressure and correlating with headache

- A bolt (ICP monitor) placed into the dura can be used to measure intrasellar pressure, which is elevated in patients with headache

<table>
<thead>
<tr>
<th></th>
<th>Patients with headaches (n = 25)</th>
<th>Patients without headaches (n = 24)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with hypopituitarism/total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MISP (mm Hg) Mean = 30</td>
<td>37 ± 12.6</td>
<td>19.8 ± 7.4</td>
<td>5.44 × 10^{-7}</td>
</tr>
<tr>
<td>Range</td>
<td>20–56</td>
<td>7–31</td>
<td>N/A</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>1.94 ± 0.59</td>
<td>2.1 ± 0.76</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Source: JCEM 85: 1789, 2000

We are working to:
- confirm that intrasellar pressure is particularly elevated in patients whose headaches improve with surgery
- identify imaging biomarkers of sellar pressure so that we can better predict from MRI whether the headache is being caused by the sellar lesion or is unrelated.
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Nonfunctional adenoma recurrence – role of extent of resection

- STR worsens recurrence rate compared to NTR or GTR
- Postop radiosurgery or radiation therapy improves PFS but still well behind outcomes seen with NTR alone
- Postop radiosurgery or radiation therapy improves PFS potentially more than that seen with GTR alone

Source: Brain Tum Res Treat 4:1, 2016
Conclusions

- **Nonfunctional Adenomas** include null cell adenomas as well as silent adenomas staining for hormones.

- **Symptomatic Outcomes**
  - **Vision** *(absolute indication for surgery by Society guidelines)*
    - Return to baseline vision unlikely in patients over age 60 AND if visual symptoms present longer than 6 months.
  - **Endocrine** *(relative indication for surgery by Society guidelines)*
    - Thyroid and male reproductive function most commonly affected axes by nonfunctional adenomas and most likely to improve
    - Thyroid/male reproductive improvement unlikely in older patients, with more severe deficits, and smaller preoperative gland volume.
  - **Headache** *(not mentioned in endocrine society guidelines for NFAs)*
    - Less likely to improve in older patients, STR

- **Recurrence**
  - More likely with silent corticotrophic adenomas and STR so consider radiation for these

Contact information

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