Functional Outcomes after Pituitary Tumor Surgery

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Overview

1. Introduction
2. Visual Outcomes after Pituitary Surgery
3. Endocrine Outcomes after Pituitary Surgery
4. Headache Outcomes after Pituitary Surgery

Focus of my neurosurgical research team at UCSF

• In 2007, we established the California Center for Pituitary Disorders (CCPD) at UCSF, integrating neurosurgical and neuroendocrine care

• Five years later, the completion of 1015 transsphenoidal surgeries at the center offered a nice benchmark for evaluation of functional outcomes after pituitary surgery.

Disclosures

None

Case breakdown by pathology (Five year interval)

- Miscellaneous: 150
- Craniopharyngioma: 50
- Rathke's Cleft Cysts: 124
- Endocrine Inactive: 381
- Endocrine Active: 340

Number of cases

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

Visual symptoms by pituitary pathology

Frequency of visual symptoms by pathology at UCSF

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 symptoms caused by pituitary tumors (reality)

Deficit | Share of patients
--- | ---
Bitemporal hemianopia | 49%
Monocular | 31%
Quadrantopia in one eye combined with quadrantopia or hemianopia in the other eye | 20%

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 Nonsecretory 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; 263, 2011

Race and age both increase duration of visual symptoms, reducing postop improvement

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.

Source: Journal of Neurosurgery 116; 1432, 2013

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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.)

Hypothalamic hormones

Anterior pituitary hormones

Downstream organ hormones

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

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:


Nature Reviews Cancer

Hormone Axis

- Central Hypothyroid (TSH, T4, T3)
- Male Hypogonadism (FSH, LH, testosterone)
- Low Growth Hormone (GH, IGF1)
- Female Hypogonadism (FSH, LH, estradiol)
- Central Hypoadrenalism (ACTH, Cortisol)

<table>
<thead>
<tr>
<th>Percentage of patients</th>
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<tr>
<td>Improvement at 6 weeks</td>
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<tr>
<td>Normalization at 6 weeks</td>
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<tr>
<td>Normalization at 6 months</td>
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Hormone Axis

- Difference between nonfunctional adenomas vs. other sellar tumors: delayed improvement unique to nonfunctional adenomas
Threshold for Surgical Correction of Pituitary Deficits

- Lower threshold beyond which surgical correction was not witnessed
  - TSH < 0.03 mIU/mL (normal at UCSF is above 0.45 mIU/mL)
  - Testosterone < 2.0 ng/dL (normal at UCSF is above 141 ng/dL)
  - Cortisol < 1 µg/dL (normal at UCSF is above 4 µg/dL)
  - IGF-1 < 35 µg/dL (normal at UCSF above 64 for females, above 87 for males)

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

Preoperative and postoperative gland volume

- 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:
Rates of headaches as a complaint versus sole complaint per pathology:

Preoperative Headache Rates:

- Misc.
- Endocrine (-) Adenomas
- Endocrine (+) Adenoma
- Craniopharyngioma
- Rathke’s cleft cysts
- Apoplexy

0% 10% 20% 30% 40% 50% 60%

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
  - 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

Headache in pituitary adenoma patients:

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

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

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.

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.

### Conclusions

- **Vision** *(absolute indication for surgery by Society guidelines)*
  - Return to baseline vision unlikely if
    - Patients over age 60 AND
    - visual symptoms have been 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 if
    - Older patients
    - More severe deficits
    - Smaller preoperative gland volume.

- **Headache** *(not mentioned in endocrine society guidelines for NFAs)*
  - More common in younger patients with Rathke’s cleft cysts
  - Less likely to improve in
    - older patients
    - STR

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