Silent Corticotroph Adenomas:
A clinico-pathologic entity distinct
from non-functioning tumors

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Outline

- Aims of Study
- Background
- Preliminary Data
- Methods
- Conclusions
Hypothesis

- Silent corticotroph adenomas (SCAs), a clinical subset of non-functioning adenomas (NFAs), are more aggressive than NFAs and Cushing’s Disease.
Aims of Study

- Determine whether SCAs recur more frequently and have a higher rate of post-operative hypopituitarism than Cushing’s Disease and NFAs.
- To validate potential pre-operative biochemical tests.
- To determine the efficacy of medical therapies in SCAs after resection of the adenoma in order to prevent recurrences.
- To closely follow SCAs for potential transformation into Cushing’s Disease.
Background

- Pituitary tumors compose 10% of intracranial tumors
- Are generally benign
- Can be hormone-producing or functionally inactive
- Classified by size: micro vs macro
- Subdivided by cell type from which they arise
NFAs (20% of pituitary tumors)
- Null-cell tumors
- No pathologic marker of hormone excess
- Are also gonadotroph adenomas (FSH/LH +)

Corticotroph adenomas\(^1\) (10% of pituitary tumors)
- ACTH +
- Have elevated cortisol and ACTH levels \(\rightarrow\) Cushing’s Disease
- 30% are silent (SCAs) and do not have hypercortisolism

Background

- SCAs are clinically silent
- Determined to be NFAs pre-operatively
- Present due to mass effects
- Often macroadenomas
- After resection, are classified as SCAs by their positive staining for ACTH
- Followed post-op for recurrences on MRIs and development of hypopituitarism

Background

- SCAs are thought to be more aggressive than either CD or NFAs
  - Study of 23 SCAs: suprasellar extension, invasion in 52%, a number with repeat surgery
  - Study of 28 SCAs vs 60 NFAs—similar regrowth rates

Background

- SCAs may have 29-57% recurrence rates\textsuperscript{2,3}
- Report of an SCA with rapid regrowth of tumor after resection\textsuperscript{5}
- Study on SCAs found that SCAs may not recur more frequently than NFAs but when they did recur, they act more aggressively\textsuperscript{4}
- Series of 5 cases of silent corticotroph carcinomas which metastasized widely\textsuperscript{6}
- A report of SCA converting post-op into Cushing’s Disease\textsuperscript{7}

\textsuperscript{7} Sano T, et al. 2002. Pituitary adenoma with “honeycomb Golgi” appearance showing a phenotypic change at recurrence from clinically nonfunctioning to typical Cushing’s Disease. 13: 125-30.
Pre-operative diagnosis of SCAs is not yet validated

Use of high molecular weight ACTH to diagnose SCA

- One patient with SCA secreted inactive high molecular weight ACTH with authentic ACTH, possibly competing with each other at the receptor and preventing Cushing’s manifestations\(^8\)

- Another report of SCA patients who have elevated ACTH with normal cortisol compared to CD with high ACTH and cortisol\(^3\)

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If can make pre-op diagnosis, can consider medical therapy either as alternative to surgery or as adjunctive therapy.

Given that SCAs may have a more aggressive course post-op, other therapies could be of benefit in preventing recurrences.
Background

- Studies in CD show questionable efficacy of agents that modulate pituitary ACTH release such as cabergoline, octreotide

- Proliferator activating receptor-gamma (PPAR-γ) ligands (e.g., rosiglitazone) may reduce cortisol levels in CD

- In NFAs, octreotide and cabergoline have limited efficacy in tumor size reduction

- No studies yet of use of these agents in treating SCAs

Background Summary

- SCAs have overall been shown to have more recurrences than NFAs or CD though no prospective trials have yet been designed.
- No evidence of pre-op diagnosis in SCAs.
- No trials of medical therapy for SCAs either pre-op or post-op.
Preliminary Studies
Preliminary Studies

- Looked at pathology database of Cedars
  - Pulled out all consecutive NFAs from 1994-2004
  - Identified 106 consecutive patients
  - 22 of 106 identified as SCAs (21%)
  - Retrospective cohort study comparing clinical and pathological characteristics of SCAs vs NFAs
  - Wilcoxon test for continuous variables
  - Fisher exact test for two group comparison
## Pre-op Manifestations

<table>
<thead>
<tr>
<th>Symptom</th>
<th>SCAs</th>
<th>NFAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>50%</td>
<td>37%</td>
</tr>
<tr>
<td>Visual field deficits</td>
<td>64%</td>
<td>61%</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>30%</td>
<td>13%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>38%</td>
<td>43%</td>
</tr>
</tbody>
</table>

Nonsignificant values
### Radiologic Characteristics

<table>
<thead>
<tr>
<th>MRI finding</th>
<th>SCAs</th>
<th>NFAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiasm compression</td>
<td>68%</td>
<td>76%</td>
</tr>
<tr>
<td>Erosion of sella</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Suprasellar extension</td>
<td>59%</td>
<td>58%</td>
</tr>
<tr>
<td>Cavernous sinus extension</td>
<td>41%</td>
<td>56%</td>
</tr>
<tr>
<td>Encasing of carotids</td>
<td>32%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Nonsignificant values
Postoperative Results

- Residual tumor on MRI:
  - 38% of SCAs vs 46% NFAs
- Recurrences:
  - 29% SCAs vs 19% NFAs (NS)
- Repeat Surgery:
  - 27% of SCAs vs 30% NFAs
- New onset post-op hypopituitarism:
  - 52% SCAs vs 27% NFAs (p<0.04)
Conclusions of Study

- Incidence of 21% of SCAs as subgroup of NFAs in Cedars database
- See some nonsignificant clinical and radiologic characteristics
- Significant difference in post-op hypopituitarism
- Suggests need for closer post-op surveillance and pituitary hormone testing
Further studies to investigate SCAs
Comparison of SCAs to CD

- Determine if SCAs behave post-op as typical Cushing’s adenomas or as NFAs.
- Will pool from pathology database 22 Cushing’s adenomas to match 22 SCAs.
- Assess development of post-op hypopit and recurrences on MRIs in Cushing’s.
- Compare data to SCAs.
Pre-op diagnosis of SCAs

- Prospective study of SCAs vs Cushing’s
- Recruit patients referred to Pituitary Center
  - 100 NFAs
  - 20 CD
- Will be classified pre-operatively as either NFAs or CD
- Will have biochemical profile to determine if NFA or CD
- Will perform functional tests on both groups
  - CRH and lysine-vasopressin test—one study showed SCA patients had exaggerated ACTH/cortisol response
  - Low dose dexamethasone study—to confirm CD

Pre-op diagnosis of SCAs

Cushing’s Disease Patients
- Elevated late night salivary cortisol
- Elevated urinary free cortisol
- Unsuppressed AM ACTH levels
- Low dose dexamethasone suppression test
- Measure high molecular weight ACTH
- Measure PRL, IGF-1, LH, FSH, TSH
- Perform CRH and lysine-vasopressin test

NFA patients
- Normal cortisol levels
- Measure bioactive ACTH
- Measure high molecular weight ACTH
- Measure PRL, IGF-1, LH, FSH, TSH
- Perform CRH and lysine-vasopressin test
Pre-op diagnosis

- Patients will then proceed to surgical resection
- Will review pathology and determine if any of the NFAs were ACTH+ on staining thus classifying them as SCAs
- Will retroactively evaluate pre-op data to determine if SCAs have a profile unique from NFAs or CD
Evaluation of Medical Therapies in SCAs

- Propose that post-operative medical therapy will reduce recurrence rates
- Will randomize the SCAs we recruited from prior study to 4 groups post-op:
  - Irradiation
  - Rosiglitazone
  - Octreotide
  - Controls
- Follow with serial MRIs, ACTH levels, and full biochemical profiles
Evaluate SCAs for conversion to CD

- Determine if SCAs have potential to convert to a hypersecretory state known as CD
- Use SCA patients recruited above
- Follow with biannual MRIs
- Measure salivary and urinary free cortisol levels
- Follow for 5 years
Conclusions

- Goal is to characterize nature of SCAs
- Determine if SCAs possess a biochemical and radiologic profile unique from NFAs and CD
- Find a means of pre-op diagnosis of SCAs
- Evaluate medical adjunctive therapies of SCAs in attempt to reduce recurrences
- Follow SCAs for potential conversion to non-silent form, CD
- Will thus determine a new class of pituitary adenomas
Thank You