Medical Management after Endonasal Surgery for Pituitary Adenomas

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Objectives: Endocrine Complications of Pituitary Surgery

1. Review normal arginine vasopressin physiology and pathophysiology
2. Describe risk factors for diabetes insipidus and an approach to treatment
3. Discuss the diagnosis and management of the Syndrome of Inappropriate Anti-diuretic Hormone
4. Review rates of post-operative hypopituitarism and predictors for anterior pituitary hormone loss or recovery
Physiology of Arginine Vasopressin Production and Action

Bichet, Daniel G. The Pituitary. 2007.
Figure 8.1. Adapted from Wilson Y, Nag N, Davern P et al. Proc Natl Acad Sci USA 2002
Triphasic Response

Timeline

<table>
<thead>
<tr>
<th>Phase</th>
<th>Diagnosis</th>
<th>Onset, days</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>Diabetes Insipidus</td>
<td>1-2</td>
<td>Hours – 5 days</td>
</tr>
<tr>
<td>Phase 2</td>
<td>SIADH</td>
<td>2-10</td>
<td>2-14 days</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Diabetes Insipidus</td>
<td>7-20</td>
<td>Permanent</td>
</tr>
</tbody>
</table>

Loh J, Verbalis JG. Endocrinol Metab Clin N Am 2008
Hypertonic Saline Triphasic Response after Craniotomy for Oligodendrogloma

Triphasic Response after Craniotomy for Oligodendrogloma

SNa (mmol/L)

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14

Time (Days after Surgery)

ddAVP, ½ NS

Fluid Restriction

Hypertonic Saline

ddAVP
Post-operative Diabetes Insipidus

• When to suspect DI:
  • Excessive urine output (>200 cc/hr for 3 consecutive hours)
  • Unusual thirst

• Diagnosis:
  • Dilute Urine: UOsm < 200 mOsm/kg or Specific Gravity < 1.005
  • Plasma Osmolarity >287 mOsm/kg, S Na >145 mmol/L

Remember to Exclude “Masqueraders”:
- Patients are thirsty due to mouth breathing and preoperative NPO
- Excretion of excess Intra-operative Intravenous fluid
- Hyperglycemia
### Predictors of Post-operative Diabetes Insipidus:
Microscopic Transsphenoidal Resection

#### All Tumor Types

<table>
<thead>
<tr>
<th></th>
<th>Overall Diabetes Insipidus</th>
<th>Permanent Diabetes Insipidus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=857)</td>
<td>18.3% (157)</td>
<td>2% (17)</td>
</tr>
<tr>
<td>Observed Intra-op CSF Leak (n=273)</td>
<td>33.3% (91)</td>
<td>4.4% (12)</td>
</tr>
<tr>
<td>Craniopharyngioma (n=29)</td>
<td>62.1% (18)</td>
<td>31% (9)</td>
</tr>
<tr>
<td>Rathke’s Cleft Cyst (n=31)</td>
<td>38.7% (12)</td>
<td>9.7% (3)</td>
</tr>
<tr>
<td>Re-operation (n=186)</td>
<td>21% (39)</td>
<td>3.2% (6)</td>
</tr>
</tbody>
</table>

#### Pituitary Adenomas

<table>
<thead>
<tr>
<th></th>
<th>Overall Diabetes Insipidus</th>
<th>Permanent Diabetes Insipidus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary Adenoma (n=743)</td>
<td>14.7% (109)</td>
<td>0.007% (5)</td>
</tr>
<tr>
<td>Microadenoma (n=227)</td>
<td>21.6% (49)</td>
<td>0.9% (2)</td>
</tr>
<tr>
<td>Macroadenoma (n=516)</td>
<td>14.3% (74)</td>
<td>0.6% (3)</td>
</tr>
<tr>
<td>Cushing’s Disease (n=180)</td>
<td>22.2% (40)</td>
<td>0.9% (1)</td>
</tr>
</tbody>
</table>

Nemer gut E et al. J Neurosurg 2005
Predictors of Post-operative Diabetes Insipidus: Endoscopic Transsphenoidal Resection

- Retrospective review of the first 126 endoscopic transsphenoidal surgeries performed at the University of North Carolina (March 2000 – August 2005).

<table>
<thead>
<tr>
<th></th>
<th>Overall Diabetes Insipidus</th>
<th>Permanent Diabetes Insipidus</th>
</tr>
</thead>
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<tr>
<td>Overall (n=110)</td>
<td>16.4% (18)</td>
<td>2.7% (3)</td>
</tr>
<tr>
<td>Observed Intra-op CSF Leak (n=19)</td>
<td>36.8% (7)</td>
<td>10.5% (2)</td>
</tr>
<tr>
<td>Craniopharyngioma (n=1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rathke’s Cleft Cyst (n=12)</td>
<td>50% (6)</td>
<td>16.6% (2)</td>
</tr>
<tr>
<td>Prior non endoscopic transsphenoidal surgery (n=14)</td>
<td>42.9% (6)</td>
<td>14.2% (2)</td>
</tr>
</tbody>
</table>

Approach to Post-operative Diabetes Insipidus

1. Routine Post-operative Monitoring for DI:
   • Record intake and fluid output on an hourly basis
   • Measure SNa every 12 hours (Urine Spec Gravity every 12 hours, alternating)

2. Expectant Management when DI occurs:
   • Allow free access to water: increased plasma osmolality stimulates thirst
   • More frequent SNa and Urine Spec Gravity monitoring

3. Treat with Desmopressin (1-deamino-8-D-arginine-vasopressin)
   • When patient cannot keep up with fluid intake
   • 1 mcg intravenous ddAVP reduces urine output within 1-2 hours, duration 6-24 hours
   • Re-dose after polyuria returns
Postoperative Syndrome of Inappropriate ADH

- **Life-threatening:** Risk of seizure and death
- Unregulated release of Arginine Vasopressin
- Rapid reduction in urine output to abnormally low volume
- Symptoms: nausea, vomiting, headache, confusion, seizure
- Self-limited: resolves once arginine vasopressin stores are depleted

Isolated Second Phase: SIADH can occur even without preceding diabetes insipidus
Risk of Symptomatic Hyponatremia after Transsphenoidal Surgery

• Systematic review of 10 case series: 2947 patients post TSS
• Rates of symptomatic hyponatremia: 3.6-19.8%

• Risk factors for Symptomatic Hyponatremia
  • Older age (3 studies)
  • Macroadenoma (1 study)
  • Pre-operative Hypopituitarism (1 study)
  • Cushing’s disease (2 studies)
  • Female gender (2 studies)

Cote et al. World Neurosurg 2016
Approach to Post-operative SIADH

1. **Routine Monitoring for SIADH:**
   - Daily SNa while hospitalized
   - Post-operative Day 7 SNa as an outpatient
   - Counsel patients to call with headaches, nausea, confusion

2. **Diagnosis of SIADH:**
   - Na <135 mmol/L (Serum Osmolality <275 mOsm/kg)
   - Inappropriately concentrated urine: UOsm >100 mOsm/kg H₂O (UNa >30 mmol/L)
   - Normal intravascular volume
   - (Exclude Cortisol, Thyroxine deficiencies and diuretic use)

3. **Management of SIADH:**
   - Generally requires ER visit or inpatient admission
   - Fluid restriction 500 mL/day less than urine output
Pituitary Hormonal Loss and Recovery After Transsphenoidal Adenoma Removal


<table>
<thead>
<tr>
<th>Rates of Pre-operative Hypopituitarism</th>
<th>n = 444 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan-hypopituitarism (including diabetes insipidus)</td>
<td>2%</td>
</tr>
<tr>
<td>Deficiency &gt; 1 anterior pituitary axes</td>
<td>70%</td>
</tr>
<tr>
<td>Gonadotroph deficiency</td>
<td>63%</td>
</tr>
<tr>
<td>Growth Hormone deficiency</td>
<td>30%</td>
</tr>
<tr>
<td>Thyrotoph deficiency</td>
<td>21%</td>
</tr>
<tr>
<td>Corticotroph deficiency</td>
<td>15%</td>
</tr>
<tr>
<td>Stalk-effect hyperprolactinemia</td>
<td>36%</td>
</tr>
</tbody>
</table>
Rates of Postoperative Hormone Recovery after Endonasal Transsphenoidal Adenoma Removal

<table>
<thead>
<tr>
<th>Rates of Post-operative Hormone Recovery</th>
<th>n = 346</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in &gt;1 anterior pituitary hormone</td>
<td>49%</td>
</tr>
<tr>
<td>Improvement in Gondadotroph function</td>
<td>30%</td>
</tr>
<tr>
<td>Improvement in Somatotroph function</td>
<td>27%</td>
</tr>
<tr>
<td>Improvement in Thyrotroph function</td>
<td>14%</td>
</tr>
<tr>
<td>Improvement in Corticotroph function</td>
<td>22%</td>
</tr>
<tr>
<td>Resolution in Stalk-effect Hyperprolactinemia</td>
<td>73% (97/133 pts)</td>
</tr>
<tr>
<td>Improvement in diabetes insipidus</td>
<td>0</td>
</tr>
</tbody>
</table>

Fatemi et al. Neurosurgery, 2008
Rates of New Postoperative Hypopituitarism after Endonasal Transsphenoidal Adenoma Removal

<table>
<thead>
<tr>
<th>Rates of Post-operative Hypopituitarism</th>
<th>n = 435</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency &gt; 1 new pituitary axes</td>
<td>5.5%</td>
</tr>
<tr>
<td>New Gonadotroph deficiency</td>
<td>2%</td>
</tr>
<tr>
<td>New Growth Hormone deficiency</td>
<td>3%</td>
</tr>
<tr>
<td>New Thyrotroph deficiency</td>
<td>1.5%</td>
</tr>
<tr>
<td>New Corticotroph deficiency</td>
<td>2%</td>
</tr>
<tr>
<td>New panhypopituitarism</td>
<td>0.002% (1 pt)</td>
</tr>
<tr>
<td>New permanent diabetes insipidus</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

Fatemi et al. Neurosurgery, 2008
Predictors of Pituitary Hormone Recovery and Loss

• Predictors of Hormone Recovery:
  • Younger age
  • No intraoperative CSF leak
  • Absence of hypertension
  • Growth Hormone secreting adenoma
  • Fewer hormonal defects pre-operatively
  • Smaller tumor size

• Predictors of Hormone Loss:
  • Tumor size
  • First half of surgical series
  • Endocrine inactive adenomas

Fatemi et al. Neurosurgery, 2008
Approach to Post-operative Pituitary Hormonal Deficiencies

1. Pre-operative Counselling:
   • ~ 24% likelihood of improvement in ≥ 1 anterior pituitary hormone (excluding stalk-effect hyperprolactinemia)
   • ~ 5% likelihood of new anterior pituitary hormonal deficiency
   • ~ 2% likelihood of permanent diabetes insipidus

2. Peri-operative hydrocortisone:
   • Experience at Penn is to treat all patients empirically for cortisol deficiency

3. 6-8 weeks Post-operatively: Reassess anterior pituitary function
In Summary:

1. Endoscopic Transsphenoidal surgery is associated with development of transient diabetes insipidus in up to 16.4%, and permanent diabetes insipidus in up to 8% of patients\(^1,2\)

2. The primary treatment for diabetes insipidus is access to free water; ddAVP is useful for severe polyuria and when patients cannot maintain oral intake

3. SIADH can be life threatening and most commonly occurs \(~4-7\) days after transsphenoidal surgery\(^3\)

4. Pre-discharge counseling and post-operative day 7 SNa can identify patients with SIADH

In Summary (continued):

5. Patients with SIADH should be fluid restricted to 500 cc less than their daily urine output and generally require hospitalization
6. 24-49% of patients recover at least one anterior pituitary hormonal deficiency postoperatively
7. ~5% of patients develop a new anterior pituitary hormone deficiency\(^4\)
8. Reassess anterior pituitary function 6-8 weeks post-operatively

Thank You!