Sellar Masses Are Not Always Pituitary Adenomas – What Are the Diagnostic Possibilities?

Brooke Swearingen, MD

Most, but not all, sellar abnormalities are pituitary adenomas. We recently reviewed our series of transsphenoidal procedures done between 1998 and 2009 to determine the incidence and characteristics of non-pituitary sellar lesions (1). Over this period, 1,469 transsphenoidal procedures were performed. One hundred sixteen cases (7.9%) were not pituitary tumors. These were divided into four major pathologic groups, including cystic lesions (53%), benign neoplasms (22%), malignancies (16%) and inflammatory lesions (9%). The most common lesions were Rathke’s cleft cysts, which comprised 42% of the series. The most common presenting symptoms were visual field abnormalities (51%) and headache (34%). Endocrine abnormalities were present in 58% of cases, most commonly hyperprolactinemia (35%), hypogonadism (23%), and hypocortisolism (23%). Presenting symptoms typically improved postoperatively, with resolution of headache in 63%, and resolution of visual symptoms in 65%.

Case History. A 37 year old female presented with six weeks of progressive headaches and sinus congestion. She was treated empirically with antibiotics for presumed sinusitis without relief. She returned with imaging shown in Figure 1C. The formal interpretation was of a pituitary adenoma with acute sphenoid sinusitis. Transsphenoidal resection was planned, but she underwent drainage of the sphenoid prior to tumor removal in an attempt to clear any residual infection. The sphenoid mucosa was biopsied and cultured; pathology showed chronic inflammation. Definitive surgery was planned after an additional two weeks of antibiotics. In the interim, she developed sudden loss of vision OD with a VIth nerve palsy. Apoplexy was suspected. Transsphenoidal debulking was performed; her vision improved and her VIth nerve palsy resolved. Pathology showed a poorly differentiated squamous cell carcinoma. Evaluation was consistent with a lung primary. Although her intracranial disease initially responded to radiation and chemotherapy, she died of widespread metastatic disease three months later.

Pathology. The major pathologic groups are shown in Figure 2. The most common etiology was non-neoplastic cystic lesions at 53%, including Rathke’s cysts (79%), arachnoid cysts (19%), and one fibrous cyst of unclear origin. Benign neoplasms were found in 22% of cases, primarily craniopharyngiomas (76% of benign neoplasms). There were 19 malignancies (16%), including five metastases (26%), and five clival chordomas (26%), as well as other isolated primary tumors. The five metastases included pancreatic islet cell, renal, lung, prostate, and one of unknown primary. There were 10 inflammatory lesions (8.6%), most commonly hypophysitis (five cases, 60%).

Patient Characteristics. The mean age was 45 years, although those with malignancies were significantly older [52 ± 16 SD years]. Cysts were twice as common in women as in men and hypophysitis was

Figure 1.
Difficult radiographic differentials (1). 1A-B: Cystic abnormalities. 1A shows a large cystic lesion with uniformly hypodense contents and no obvious solid component, suggestive of a Rathke’s cleft cyst; at operation biopsy of the wall was consistent with a craniopharyngioma. 1B also shows a large cystic lesion with heterogeneous contents, bright on T1 with and without contrast and a thickened enhancing wall, suggestive of a craniopharyngioma; biopsy of the lining showed this to be a Rathke’s cyst. 1C-D: Malignancies masquerading as adenomas. 1C shows an MRI read initially as showing a macroadenoma with sphenoid sinusitis; at operation it proved to be a poorly differentiated carcinoma of lung origin. 1D shows an MRI initially read as showing a macroadenoma; at operation initial pathology was read as an adenoma with dense fibrosis; upon recurrence it was found to have de-differentiated into a malignant primary fibrosarcoma of the sella.
more common in women as well (4/5 cases, 80%). Fifty-seven patients had formal visual field examinations, and 51% were impaired, although it is likely that these examinations were ordered in those patients felt to have abnormalities (Table 1). Ophthalmologic findings were most common in patients with malignancies, where 47% had diplopia or ptosis. The most common endocrine symptoms were amenorrhea (17%), galactorrhea (13%), and male hypogonadism (18%). The most common endocrine dysfunction was hyperprolactinemia (34%) followed by hypogonadism and central hypothyroidism (Table 2). Only one patient (with a malignancy) presented with diabetes insipidus.

**Radigraphic Characteristics** Although radiographic characteristics varied by diagnosis, the differential diagnosis in many cases was difficult. Examples are seen in Figure 1. In particular, the differential diagnosis of cystic abnormalities was unclear, and it was not unusual for malignancies to be confused with benign adenomas. Most Rathke’s cleft cysts exhibited some degree of rim enhancement, as opposed to the absence of rim enhancement seen in arachnoid cysts, which contained fluid of CSF density. Although most craniopharyngiomas contained an enhancing solid component, this was not always true, and the differential between craniopharyngioma and Rathke’s cysts could in some cases be made only on pathologic analysis. The malignancies were generally widely invasive and usually suspected preoperatively, but in four cases (fibrosarcoma, osteosarcoma, squamous carcinoma, and lung metastasis), the preoperative radiographic diagnosis was of pituitary adenoma. The inflammatory lesions were characterized by homogeneous enhancement, indistinct from normal gland.

**Outcome** All patients underwent either transsphenoidal biopsy or attempted resection, depending upon the degree of invasion and suspected diagnosis. Biopsy was performed primarily in those patients with inflammatory lesions or invasive malignancies. Patients with cystic lesions underwent drainage as opposed to attempted resection of the cyst wall. While there were a number of radiographic recurrences, 6/61 (10%) patients with cysts required re-operation for repeat drainage. Cystic craniopharyngiomas underwent a combination of drainage and resection, usually followed by radiation treatment, and 7/18 (39%) required re-operation for cyst recurrence.

Headache resolved in 25/40 (63%) patients after initial presentation, most commonly after cyst drainage. Visual complaints improved in 65%, again most commonly in those with cysts (80%). Of the 64 endocrine

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**Table 1**
Initial clinical presentation in 116 patients with sellar masses other than pituitary adenomas (1).

<table>
<thead>
<tr>
<th>Etiologic groups</th>
<th>% of pts with symptoms</th>
<th>MAL (n=20)</th>
<th>CYS (n=62)</th>
<th>BEN (n=24)</th>
<th>INF (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative sign/symptom</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEUROPSYCHIATRIC COMPLAINTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>33 (29)</td>
<td>5 (21)</td>
<td>2 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>8</td>
<td>0</td>
<td>8 (13)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>4</td>
<td>1 (5)</td>
<td>2 (3)</td>
<td>2 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Cognitive complaints</td>
<td>3</td>
<td>1 (5)</td>
<td>2 (3)</td>
<td>1 (10)</td>
<td></td>
</tr>
<tr>
<td>OPHTHALMOLOGIC DYSFUNCTIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binocular vision/visual loss</td>
<td>22</td>
<td>5 (25)</td>
<td>15 (24)</td>
<td>6 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Diplopia/Pins (documentation of cranial nerve pals)</td>
<td>9</td>
<td>9 (45)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Visual field impairment on testing*</td>
<td>51</td>
<td>5 (71)</td>
<td>E (39)</td>
<td>11 (68)</td>
<td>0</td>
</tr>
<tr>
<td>GENERAL</td>
<td>Fatigue/weakness</td>
<td>10</td>
<td>2 (10)</td>
<td>7 (11)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Galactorrhea</td>
<td>13</td>
<td>0</td>
<td>6 (14)</td>
<td>1 (8)</td>
<td>2 (33)</td>
</tr>
</tbody>
</table>

Percentages are given in parentheses.
* Percentage of visual field impairment was calculated on 57 available examinations. These are distributed as follows: 33 in group CYS, 7 in group MAL, 16 in group BEN, 1 in group INF
** p<0.05 vs. the other groups
† p<0.001 vs. group BEN or CYS
‡ p<0.05 vs. group INF

**Table 2**
Pituitary function before and after transsphenoidal surgery (1).

<table>
<thead>
<tr>
<th>Cases of pituitary disturbances</th>
<th>MAL (n=20)</th>
<th>CYS (n=62)</th>
<th>BEN (n=24)</th>
<th>INF (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hypoestrogenotism</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>8</td>
<td>35</td>
<td>18</td>
</tr>
<tr>
<td>No. of new cases after TSS (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypoestrogenotism</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Permanent DI</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>40±34</td>
<td>35±30</td>
<td>67±36*</td>
<td>25±19</td>
</tr>
</tbody>
</table>

Follow-up is expressed as mean ± SD. DI: diabetes insipidus.

Impairment of more than one axis was observed in some patients for each group, as follows:
- group MAL (two pts. with two axes altered, one pt. with one axis altered)
- group CYS (five pts. with two axes altered; three pts. with one axis altered)
- group BEN (two pts. with two axes altered, one pt. with all axes altered)
- group INF (one pt. with two axes altered; one pt. with three axes altered)

*p<0.05 vs. group MAL
‡ p<0.01 vs. group CYS

Other includes chordomas, germinomas, osteogenic sarcoma, fibrosarcoma, ependymoma, hyperplasia, hamangioma, infection, papilloma, squamous carcinoma, fibrous dysplasia, sphenoid sinusitis, sinonasal undifferentiated carcinoma and unspecified cyst

Figure 2
Diagnosis in 116 patients with sellar masses other than pituitary adenomas

- Rathke’s cysts
- Craniopharyngiomas
- Arachnoid cysts
- Hyphopituitarism
- Metastasis (pancreas, kidney, lung, prostate)
- Chordomas
- Meningiomas

*Other includes chordomas, germinomas, osteogenic sarcoma, fibrosarcoma, ependymoma, hyperplasia, hamangioma, infection, papilloma, squamous carcinoma, fibrous dysplasia, sphenoid sinusitis, sinonasal undifferentiated carcinoma and unspecified cyst


**continued on page 4**
Cardiovascular Effects of Acromegaly

Alexander Faje, MD

Standardized mortality rates are approximately twofold higher in patients with acromegaly compared to the general population (1). Cardiovascular and cerebrovascular disease accounts for nearly 60% of deaths among patients with acromegaly (2). Advances in the treatment of acromegaly have improved the clinician's ability to obtain disease remission. Biochemical normalization, as assessed by levels of growth hormone (GH) and/or insulin-like growth factor type 1 (IGF-I) is associated with reductions in cardiovascular and all-cause mortality (Figure 1) [1-5].

In vitro studies support a link between GH/IGF-I and the cardiovascular system. IGF-I receptors are expressed on the cell surface of cardiomyocytes and endothelial cells (6-7). Stimulation of cardiomyocytes by IGF-I results in cell hypertrophy, increased contractility, and inhibition of apoptosis (8-11). Growth hormone may also affect connective tissue in the cardiovascular system by induction of metalloproteinase gene expression and modulation of the extracellular matrix (12-13).

The cardiac effects of acromegaly are initially manifested as a hyperkinetic state characterized by greater myocardial contractility and increased cardiac output. Further exposure to excess amounts of GH can result in concentric biventricular hypertrophy and impairment of diastolic function. Cardiac output during exercise and ultimately, at rest, may be reduced (14). Additionally, cardiac valve abnormalities are prevalent in patients with acromegaly (15), and disturbances in cardiac conduction appear to be more common compared to controls (16).

Effects on collagen deposition and the extracellular matrix may affect blood vessel morphology and function in acromegaly. Mean aortic root diameters are greater in acromegaly, and vessel enlargement may progress to aortic ectasia in some patients (17-18). Some studies have suggested an increased prevalence of intracranial aneurysms in acromegaly (19-20). Vascular function may also be altered in patients with acromegaly, contributing to increased arterial stiffness and hypertension (21-23).

Cardiovascular disease in patients with acromegaly is likely exacerbated by the high prevalence of comorbid factors. Hypertension is present in nearly one-half of patients (24) and compounded by the frequent presence of sleep apnea and diabetes (25-26). Altered levels of factors regulating coagulation and fibrinolysis may also promote the development of vascular complications (27).

Although there is an elevated incidence of hypertension and diabetes among patients with acromegaly, the relationship between acromegaly and coronary artery disease (and GH excess per se and atherosclerosis) is not well-defined. Small studies suggest that coronary artery calcification does not correlate with GH excess and that acromegaly does not specifically confer a high risk of coronary artery disease (28-29). Data regarding carotid intima-media thickness are varied (14).

Cardiovascular outcomes are predicted by the severity and duration of acromegaly. Higher cumulative disease burden (as assessed by elevated serial IGF-I values) is associated with the presence of cardiomyopathy, and disease duration positively correlates with left ventricular mass index and the prevalence of regurgitant valvular disease (30-32). Both the duration of symptoms and the degree of GH elevation are independent predictors of overall survival in patients with acromegaly (3). These results suggest that achieving earlier disease remission may potentially improve clinical outcomes. A small study utilizing octreotide-LAR suggested that the cardiac effects of acromegaly were more commonly reversed after remission in younger patients with shorter disease duration (32).

The effective treatment of acromegaly produces secondary cardiovascular improvement from changes in blood pressure, blood glucose homeostasis, and lipid profile parameters yielding direct cardiovascular benefit. Studies after surgery demonstrate improvements in cardiac function, left ventricular mass, and endothelial function (33-34). Similar benefits are observed following medical therapy. Treatment with somatostatin analogues (SSA) can reverse changes in cardiac morphology and performance. Greater benefits are observed in younger patients and those with larger reductions in GH and/or IGF-I levels (32,35). SSA may exert additional direct effects on the heart. Genes for somatostatin receptor subtypes 1, 2, 4, and 5 are expressed in cardiac tissue (36). Octreotide slows cardiac conduction velocity (37), and treatment with lanreotide may decrease arrhythmias in patients with acromegaly (38).

Data regarding pegvisomant, a GH receptor antagonist, are limited. One study demonstrated improvement in left ventricular mass index and diastolic and systolic performance after 18 months of treatment (39).

**Figure 1**
Cardiovascular mortality in patients with acromegaly according to random serum GH concentration. (Dotted line represents survival in the general population.)

The dopamine agonist cabergoline may occasionally be effective in the treatment of acromegaly [40]. Although high doses of cabergoline have been linked to cardiac valvular disease in patients treated for Parkinson’s disease, therapy with lower doses in patients with acromegaly does not appear to increase the risk of valve abnormalities [41].

Growth hormone deficiency (GHD) is not uncommon after definitive treatment of acromegaly [42]. Patients cured of acromegaly with subsequent GHD have increased levels of visceral fat and high-sensitivity C-reactive protein. These changes are reversed by GH replacement, however, safety has not yet been clearly established [43-45].

GH excess, through direct and indirect mechanisms, results in maladaptive functional and morphologic alterations in the cardiovascular system. Likewise, GHD after cure of acromegaly is associated with a metabolic phenotype which confers higher cardiovascular risk. Restoration of normal GH levels can ameliorate or reverse the cardiovascular effects of GH excess and deficiency.

References

Patients may qualify for research studies in the Neuroendocrine Clinical Center. We are currently accepting the following categories of patients for screening to determine study eligibility. Depending on the study, subjects may receive free testing, medication and/or stipends.

<table>
<thead>
<tr>
<th>SUBJECTS</th>
<th>STUDIES</th>
<th>CONTACT</th>
</tr>
</thead>
</table>
| Adults with GHD | • Diagnostic testing for GHD  
• Assessing bone microarchitecture | Beverly MK Biller, MD  
Karen Pulaski Liebert, RN  
Nicholas Tritos, MD |
| Adolescent and young adult athletes | • Investigating impact of hormonal alterations on menstrual function and bone density | Madhu Misra, MD  
Anne Klibanski, MD  
Kathryn Ackerman, MD |
| Obese adolescent girls | • Investigating impact of growth hormone on body fat distribution and metabolic function | Madhu Misra, MD  
Anne Klibanski, MD |
| Adolescent girls with anorexia nervosa | • Investigating the impact of new therapies on bone density | Madhu Misra, MD  
Anne Klibanski, MD  
Kathryn Ackerman, MD |
| Women with anorexia nervosa | • New therapies  
• Cross-sectional bone density study | Karen K Miller, MD  
Anne Klibanski, MD  
Pouneh Fazeli, MD  
Elizabeth Lawson, MD |
| Women ages 18-40 with a history of anorexia nervosa | • Investigating hormones and brain circuitry involved in appetite | Elizabeth Lawson, MD  
Anne Klibanski, MD |
| Men and women with active or treated acromegaly | • Quality of life  
• Cross-sectional bone density study  
• Assessing bone microarchitecture | Karen K Miller, MD  
Pouneh Fazeli, MD  
Karen Pulaski Liebert, RN  
Nicholas Tritos, MD |
| Girls and women with current anorexia nervosa or a history of anorexia nervosa, ages 10 and up | • Investigating genetics of appetite-regulating and stress hormones | Elizabeth Lawson, MD  
Karen K Miller, MD  
Anne Klibanski, MD  
Madhu Misra, MD |
| Healthy girls and women, ages 10 and up | • Investigating genetics of appetite-regulating and stress hormones | Elizabeth Lawson, MD  
Karen K Miller, MD  
Anne Klibanski, MD  
Madhu Misra, MD |
| Healthy normal-weight and obese men | • Effect of oxytocin on caloric intake | Elizabeth Lawson, MD |
| Healthy normal-weight women | • Cross-sectional bone density study | Pouneh Fazeli, MD  
Anne Klibanski, MD |
| Healthy slightly overweight men and women | • Investigating the effects of fasting on adipose tissue distribution | Pouneh Fazeli, MD |
| Obese women | • Cross-sectional bone density study | Pouneh Fazeli, MD  
Anne Klibanski, MD |
| Obese men and women | • Investigating the effect of acipimox, a medication to decrease free fatty acids, on skeletal muscle mitochondria | Hideo Makimura, MD |
| HIV positive men and women with and without metabolic abnormalities | • Assessment of coronary artery atherosclerosis  
• Growth hormone and growth hormone releasing hormone  
• Assessment of long-term GHRH  
• Assessment of eplerenone on metabolic abnormalities  
• Assessment of menopausal transition  
• Statin therapy for coronary plaque  
• Assessment of effects of Quad therapy on coronary plaque | Steven Grinspoon, MD  
Janet Lo, MD  
Katie Fitch, FNP  
Takara Stanley, MD  
Suman Srinivasa, MD  
Markella Zanni, MD |
| Adults with moderate-to-severe psoriasis about to be started on etanercept (Enbrel) by their treating dermatologist | • Assessment of cardiovascular and metabolic health | Markella Zanni, MD  
Steven Grinspoon, MD |
| Adults with newly diagnosed HIV who about to be started on Stribild (Quad) by their treating infectious disease doctor | • Assessment of cardiovascular and metabolic health | Markella Zanni, MD  
Steven Grinspoon, MD |

*The Neuroendocrine Clinical Center is involved in many different research studies. Types of studies and enrollment status changes frequently, so please call our office (617-726-3870) or check our webpage (massgeneral.org/neuroendocrine) for more information about potential studies which may not be listed here.*
Facilities
The Neuroendocrine Center is located on the 1st floor (Suite 112) of Zero Emerson Place at the Massachusetts General Hospital. A test center is available for complete outpatient diagnostic testing, including ACTH (Cortrosyn) stimulation; insulin tolerance; CRH stimulation; oral glucose tolerance and growth hormone stimulation testing. Testing for Cushing’s syndrome can also be arranged, including bilateral inferior petrosal sinus ACTH sampling for patients with ACTH-dependent Cushing’s syndrome.

Neuroendocrine Clinical Conference
A weekly interdisciplinary conference is held to discuss all new patients referred to the Neuroendocrine Center and to review patient management issues. It is a multidisciplinary conference, attended by members of the Neuroendocrine, Neurology, Neurosurgery, Psychiatry and Radiation Oncology services. Physicians are welcome to attend and present cases.

Physicians’ Pituitary Information Service (PPIS)
Physicians with questions about pituitary disorders may contact the PPIS at (617) 726-3965 within the Boston area or toll free at (888) 429-6863, or e-mail to pituitary.info@partners.org.

Scheduling
Outpatient clinical consultations can be arranged by calling the Neuroendocrine Center Office at (617) 726-7948.