Neurological Complications of Tumors of the Sella and Parasellar Region

Thomas N. Byrne, MD

Pituitary tumors and other tumors arising in the sella and parasellar region can cause neurological complications when they extend to compress or invade surrounding structures. These complications may occur either at presentation or during follow-up and can be classified into three categories based upon the anatomy: 1) Cranial nerves II, III, IV, VI and the first and second division of V; 2) Hypothalamus and 3) Cerebral. This brief review discusses the clinical manifestations of these neurological disorders.

Cranial Nerve Deficits:

The most common neurological complications of such tumors are cranial nerve deficits. In the case of pituitary apoplexy they can evolve over hours or days but in most pituitary adenomas or other tumors such as meningioma or craniopharyngioma the evolution can be indolent, often over months. The bedside tests below do not substitute for neuro-ophthalmological evaluation but when they are abnormal they usually indicate visual pathway dysfunction.

Compression of the optic chiasm due to suprasellar extension of pituitary tumors classically causes bitemporal superior visual field deficits initially. However, unilateral visual field loss or reduced visual acuity may predominate if the chiasm is posteriorly fixed (15% of individuals),[1] or if the tumor is anterior such as in the case of a tuberculum sella meningioma.[2] A simple bedside test for visual fields is for the patient to cover one eye at a time and for the examiner to show fingers simultaneously in the upper nasal and temporal fields and then repeat the same in the lower half paying particular attention for a subtle superior bitemporal visual field cut which, again, is the most common.

Compression of the optic nerves may also lead to dyschromatopsia (loss of color vision). A simple test is as follows: If the patient is asked to look at a brightly colored tie, scarf or other object with each eye independently and there is a difference in the brightness of the color it is indicative of an afferent visual pathway deficit such as occurs with an optic neuropathy. Testing for a relative afferent pupillary deficit is another simple bedside test that is sensitive for assessing optic nerve dysfunction although it has only variable sensitivity for optic chiasm dysfunction. In this test, sometimes called the swinging flashlight test, the light is shown into one eye at a time and when the light is swung from the normal eye to the affected eye both pupils dilate. A positive test is sometimes called a Marcus Gunn pupil; sometimes mistakenly

The macroprolactinoma case presented on Page 5 by expert Mass General pituitary surgeon Brooke Swearingen shows an interesting and rare neurological complication of medical treatment.

considered a specific a sign of multiple sclerosis, it can occur in other causes of optic neuropathy.

Injury to cranial nerves III, IV, VI usually causes diplopia. Compression of the third cranial nerve may also cause ptosis and a dilated pupil. Compression of the first division of cranial nerve V may cause pain and/or numbness of the ipsilateral forehead and nose. Probably the most sensitive clinical test of the sensory division of the first division of the Vth cranial nerve is the corneal response; by comparing the two sides one can often determine whether the

pain in the region is due to injury of the nerve; if the first cornea tested appears to be more sensitive be careful it is not a false positive result that is due to the cotton being moist and thus less irritating with the second cornea. The second division of cranial nerve V innervates the skin over the maxillary area.   Remarkably, invasion of the cavernous sinuses demonstrable on MRI of pituitary adenomas may not cause dysfunction of these cranial nerves, although inflammatory and other neoplastic processes often cause dysfunction. The reason for this is unclear although it may be due to the fact that pituitary adenomas are usually very indolent and the nerves may have an opportunity to adapt. In contrast, diplopia and ptosis may be the initial presentation (often with headache) of pituitary apoplexy, which is typically more rapid in onset.

Hypothalamic Dysfunction:

The hypothalamus controls a multitude of functions, among them are hunger and satiety, memory and sleep-wake cycles.

Hyperphagia and weight gain are common manifestations of hypothalamic dysfunction that may occur as a result of tumor invasion or surgery especially in the case of craniopharyngiomas. In the study of 10-year follow-up of craniopharyngiomas by Karavitaki,[2] hyperphagia or excessive weight gain was present in 39%. Weight gain is believed to be due to central leptin insensitivity.[3] Leptin, released by adipose cells, stimulates hypothalamic neurons to release anorectic neuropeptides and suppress orexigenic peptides.[4]

There are a number of sequelae to hyperphagia and obesity. Among them is obstructive sleep apnea which, in turn, can lead to cognitive dysfunction through daytime sleepiness and inattention. This cause of cognitive dysfunction is important to recognize as it may be remediable through weight loss or devices that successfully

treat sleep apnea. Another cause of memory loss may be due to disruption of the pathway connecting the hippocampi to the mammillary bodies. In the retrospective study by Karavitaki cited above, at 10 years following diagnosis of craniopharyngioma about a quarter of patients were unable to work at their previous occupation or were behind their expected school level. Some of these cases may have been due to other cerebral dysfunction but many were primarily secondary to hypothalamic dysfunction.

Another cause of daytime sleepiness is disrupted circadian rhythms and melatonin deficiency which is a biomarker for the circadian pacemaker located in the hypothalamus.[5, 6] Lipton and colleagues recently demonstrated in three craniopharyngioma survivors that although they had normal sleep architecture on polysomnography there was a significant reduction in plasma melatonin levels throughout the 24-hour day but especially during the night.[5] The authors suggest that the low melatonin levels may reflect disruption of the normal circadian arousal systems of the hypothalamus which normally leads to a rise in melatonin at night. In such patients, they suggest that daytime hypersomnolence may respond to exogenously administered melatonin at night which can assist in causing sleep. This treatment has been reported to show some success.[7, 8] They also suggest measurement of 24-hour urine 6-hydroxymelatonin sulfate, aggressive weight reduction, treatment of obstructive sleep apnea and exposure to bright light on awakening.

Cerebral Dysfunction:

When the tumor is in the suprasellar location cerebral dysfunction can occur. Again, in the study of 121 patients with craniopharyngiomas,[2] 23% presented with hydrocephalus; of course tumors of any histology that are in the suprasellar location may be associated with hydrocephalus at presentation or at recurrence by compression of the third ventricle or aqueduct. Many of these patients have visual field deficits if the optic chiasm is compressed but this may not always be the case and the clinical presentation can be quite protean. Some patients will have gait abnormalities and frontal lobe dysfunction with cognitive impairment, lack of initiative and inattention, often with a paucity of focal neurological signs. Since these patients may not have prominent focal neurological signs they resemble those with metabolic encephalopathy as is common in patients with endocrinopathies, thereby misleading the clinician. Such patients have been said to have the so-called three M syndrome "Minimal focal signs, maximal disability and midline lesion." This is important to bear in mind while following patients with tumors in this location since the clinical evolution can be mistakenly attributed to an evolving endocrinopathy.

Suprasellar and lateral extension of tumors through or above the cavernous sinus may cause compression of the medial temporal lobe without causing cranial neuropathies or other focal neurological signs. The medial temporal lobe is among the most epileptogenic regions and patients may develop complex partial seizures with or without grand mal seizures. We have seen patients who report episodes of déjà vu, olfactory hallucinations or just feeling out of touch with their environment that were due to seizures. One clue that these are seizures is that patients often feel quite fatigued immediately following these events. Finally, since the hippocampi in the medial temporal lobes serve recent memory function, injury to these structures can cause memory loss. In patients who have received radiotherapy to the sella region, radiation injury to the temporal lobe(s) can occur with similar consequences.

In summary, pituitary adenomas and other neoplasms extending into the suprasellar and parasellar regions can cause a host of neurological problems that impact significantly on the well-being of the patient. Importantly, many of these are treatable which is a great incentive to their early diagnosis.

References

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Growth Hormone (GH) Deficiency after Definitive Therapy for Acromegaly: Part II – Effects of GH Replacement

Karen K. Miller, MD

In the last issue of the Bulletin, we presented data demonstrating an impaired quality of life in patients who have developed growth hormone deficiency (GHD) after definitive treatment for acromegaly, and we raised the question of whether such patients might benefit from growth hormone (GH) replacement. We now have a partial answer to that question, in the form of the recently published results of our randomized, placebo-controlled study which demonstrated benefits to body composition and quality of life, with few side effects[1].

In this study, thirty patients (17 women and 13 men) who developed GHD after definitive treatment of acromegaly were randomized to receive GH replacement or placebo for six months. GHD was defined as a stimulated GH level of less than 5 ng/ml (by growth hormone releasing hormone and arginine or insulin tolerance test) or IGF-1 level below the lower limit of normal in the presence of at least three other pituitary hormone deficiencies. The mean daily GH dose at six months was modest at 0.58±0.26 mg, and this raised the insulin-like growth factor (IGF-1) standard deviation score from a mean of -1.98±0.60 (approximately two standard deviations below mean normal for age) to a mean of -0.60±1.1 (still below average for age). This relatively low replacement dose of GH resulted in beneficial changes to body composition, including a mean 1.5 kg increase in lean body mass and a mean 15% reduction in visceral fat compared with the pre-study state (a 16.5% reduction compared with placebo) (Figure 1). The potential significance of the latter finding lies in the strong links that have been firmly established between visceral adiposity and cardiovascular risk. Another indicator of cardiovascular risk, high-sensitivity C-reactive protein, also decreased in the group that received GH compared with placebo, but no significant effect of GH on a number of other cardiovascular risk markers measured, including cholesterol and carotid intimal-medial thickness, was observed. It is important to note that the study could not determine whether GH had any effect on the incidence of actual cardiovascular events. Quality of life, as measured by three questionnaires, was also shown to be favorably affected by GH. This included improvement of five of eight subscales of the widely used Short-Form Health Survey (SF-36) (Figure 2). Of potential importance was a substantial improvement in energy and fatigue in a population for which this is a common complaint.

An important question is whether GH replacement therapy is safe in a population with an increased lifetime GH exposure and higher-than-average baseline cardiovascular and metabolic risks. Our results were reassuring in this regard, but not all studies of GH administration in patients who have developed GHD after treatment of acromegaly have supported our findings. We observed no increase in measures of insulin resistance or glucose control and
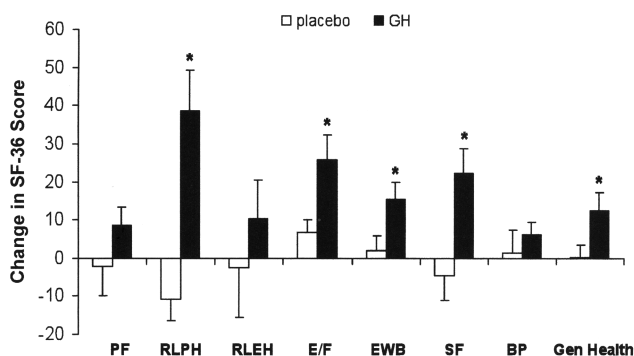

Figure 1.
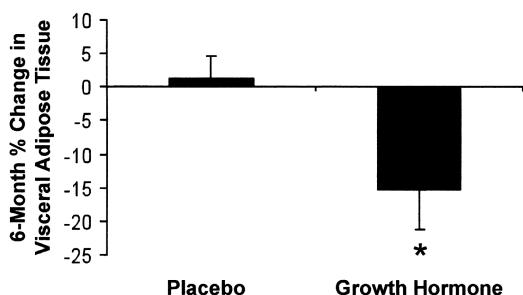
GH replacement resulted in a significant decrease in visceral adiposity compared with placebo. *, p<0.05.

From Miller KK, et al. 2010. Growth Hormone Deficiency After Treatment of Acromegaly: A Randomized, Placebo-controlled Study of Growth Hormone Replacement. J Clin Endocrinol Metab. 95:567-77. *Copyright 2010, The Endocrine Society.*

Figure 2.

GH replacement resulted in improvements in quality of life in five of eight SF-36 questionnaire subscales. Higher scores reflect a better quality of life. PF, physical function; RLPH, role limitations due to physical health; RLEH, role limitations due to emotional health; E/F, energy and fatigue; EWB, emotional wellbeing; SF, social functioning; BP, bodily pain; Gen Health, General Health.

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few side effects to the medication. We did not observe a higher rate of edema, arthralgias or carpal tunnel syndrome symptoms in the GH group compared with placebo. In addition, no subject in either group experienced any serious adverse events. The latter finding is consistent with reports of two open-label studies[2, 3], but contrasts with that of an open-label study published by Norrman *et al.* in 2008[4]. In that study, of the ten patients with prior acromegaly receiving GH, one experienced a myocardial infarction and two experienced cerebral vascular accidents. Whether GH administration was a contributory factor to the occurrence of these events is unclear.

In summary, our randomized, placebo-controlled study demonstrated beneficial changes in body composition, including visceral adiposity, and quality of life in patients who developed GHD after definitive treatment of acromegaly. Our study results were reassuring with respect to the safety of prescribing GH to this population, but another published study reported a very high incidence of cardiovascular and cerebrovascular events. Therefore, we recommend refraining from prescribing GH in patients with a history of acromegaly at particularly high cardio-vascular risk until additional safety data are available.

References

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3. van der Klaauw AA, et al. Pituitary. 2009; 12:339-46.
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Cases of the Neuroendocrine Clinical Center: Tethered Chiasm

Brooke Swearingen, MD

A 42 year old male presented with a two year history of headaches and visual loss. Formal visual fields showed a bitemporal hemianopsia. Endocrine testing showed a prolactin of 1300 ng/ml (nl < 15). An MRI was performed which was read as showing "a large cystic macroadenoma with a central septation and chiasm compression" (Figure 1). He was begun on cabergoline at 0.5 mg biweekly by his PCP for a presumed macro-prolactinoma. One week later, he presented to the Emergency Room with the report of worsening headaches and progressive visual loss. Apoplexy was suspected and a CT scan was performed (he was unable to tolerate an MRI) which was read as showing a cystic sellar mass, without hemorrhage. He was referred to neurosurgery.

Review of imaging. Review of his imaging studies suggested that his sella was, in fact, dramatically enlarged but predominantly empty, with a small amount of tumor in the floor of an enlarged sella. There was no "cystic macroadenoma". The gland had descended into the enlarged sella, with traction on the pituitary stalk and tethering of the chiasm inferiorly (Figure 1).

Diagnosis. 1. Tethered chiasm. 2. Macroprolactinoma

Pathophysiology. The bitemporal defect was the result of traction on the chiasm with prolapse into the enlarged sella. There was no compression from the adenoma. His vision deteriorated after initiation of dopamine agonist treatment as the prolactinoma decreased in size, shrinking into the enlarged sella, leading to further traction on the chiasm.

Course of treatment. The cabergoline was discontinued with stabilization of his visual deficit. He then underwent transsphenoidal chiasmopexy, with the floor of the enlarged sella reconstructed using silastic plates. The gland was elevated extradurally by the sellar reconstruction, relieving the traction on the pituitary stalk (Figure 2).

Follow-up. His vision improved after the chiasmopexy, although the bitemporal defect persisted. Cabergoline was resumed at a low dose; his prolactin level decreased to 21 ng/ml. Follow-up MR imaging has shown stabilization of the residual tumor without change in the sellar reconstruction; traction on the chiasm remains relieved.

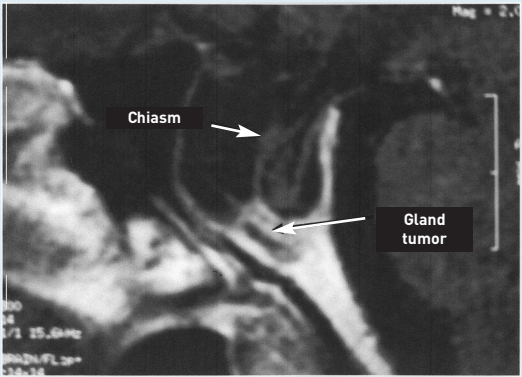# Cases of the Neuroendocrine Clinical Center: Tethered Chiasm

Preoperative Scans

Figure 1A.
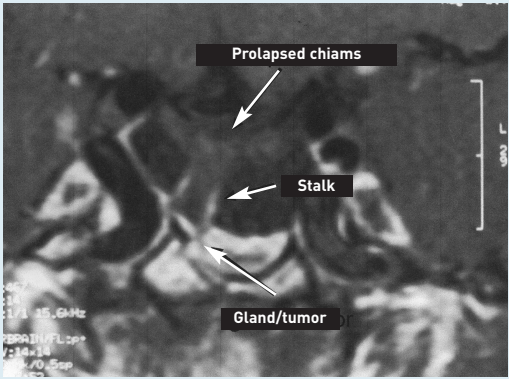
Coronal view, T1 with contrast, showing largely empty sella filled with CSF, prolactinoma in floor of sella, prolapse of chiasm with pituitary stalk under tension.
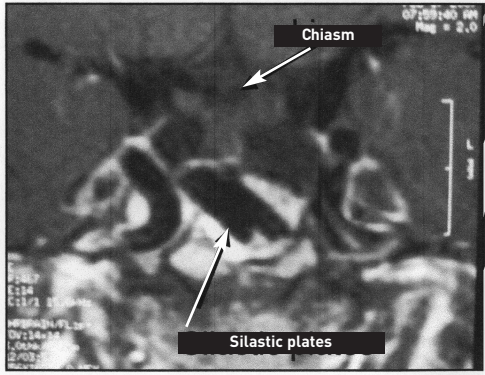
Figure 1B.

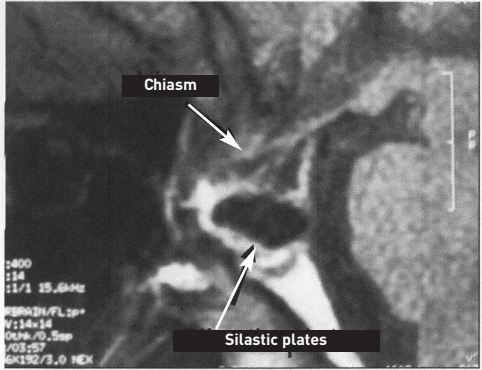Sagittal view showing enlarged empty sella with prolapsed chiasm.

Postoperative Scans

Figure 2A.

Post-operative view showing placement of silastic plates, un-tethering of stalk with elevation of chiasm

Figure 2B.

Postoperative view, sagittal.

RESEARCH STUDIES AVAILABLE

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.

SUBJECTS	STUDIES	CONTACT 617-726-3870
Newly diagnosed acromegaly	Evaluating pre- and post-operative medical treatments	Karen Pulaski-Liebert, RN Dr. Beverly M.K. Biller Dr. Anne Klibanski Dr. Pouneh Fazeli
Adolescent and young adult athletes	• Investigating impact of hormonal alterations on • menstrual function and bone density	Dr. Madhu Misra Dr. Anne Klibanski
Obese adolescent girls	• Investigating impact of growth hormone on body fat • distribution and metabolic function	Dr. Madhu Misra Dr. Anne Klibanski
Adolescent girls with anorexia nervosa	• Investigating the impact of new therapies on bone density	Dr. Madhu Misra Dr. Anne Klibanski Dr. Karen K. Miller
Women with anorexia nervosa	• New therapies	Dr. Karen K. Miller Dr. Anne Klibanski
Women ages 18-28 with a history of anorexia nervosa	• Investigating hormones and brain circuitry involved in appetite	Dr. Elizabeth Lawson Dr. Anne Klibanski
Men, ages 18-45	• Investigating body weight and GH secretion • GH treatment in abdominal obesity	Dr. Karen K. Miller
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	Dr. Elizabeth Lawson Dr. Karen K. Miller Dr. Anne Klibanski Dr. Madhu Misra
Healthy girls and women, ages 10 and up	• Investigating genetics of appetite-regulating and stress hormones	Dr. Elizabeth Lawson Dr. Karen K. Miller Dr. Anne Klibanski Dr. Madhu Misra

Obese men and women	• Use of GHRH, a growth hormone secretagogue,
	  to increase endogenous GH levels, improve fat
	  distribution and lipid profile
		Dr. Hideo Makimura
		Dr. Steven Grinspoon

Overweight children	• Effects of exercise on mitochondrial function	Dr. Amy Fleischman Dr. Steven Grinspoon
HIV positive men and women with and without metabolic abnormalities	• Assessment of coronary artery atherosclerosis • Lifestyle modification strategies, including exercise and insulin sensitization • Short-term GH • Statin therapy for coronary plaque	Dr. Steven Grinspoon Dr. Janet Lo Katie Fitch, ANP Dr. Takara Stanley

NEUROENDOCRINE CLINICAL CENTER **BULLETIN**

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SERVICES AVAILABLE

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 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
Physicians with questions about pituitary disorders may contact Dr. Biller or Dr. Klibanski 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.