

Technologic Advance: Intraoperative MRI used for Pituitary Tumors at MGH

by Brooke Swearingen, M.D.

A new intraoperative MRI has recently been installed in the MGH neurosurgical operating suite. Unlike standard MRI facilities, this is a portable machine which is designed to be used in an operating room. It is small enough to be stored under the operating table, and can be wheeled out when needed. Dr. Robert Martuza, Chief of Neurosurgery at MGH, calls it "The MRI equivalent of a portable x-ray" and explains its importance as follows. "Physicians now can view images during the actual operation, rather than having to look at images made preoperatively and postoperatively. The MRI offers real-time visualization during all stages of brain surgery, so that neurosurgeons can plan the path of the surgery at every point."

The MR scanner will allow images to be obtained during and after neurosurgical procedures, both to guide the surgeon during the operation, and to provide information on the extent of residual tumor in those cases where visual cues are inadequate. It will be especially useful in pituitary surgery, since transsphenoidal procedures provide a relatively limited exposure through the operative microscope, and it can be difficult for the surgeon to determine the extent and location of any residual tumor. It is now possible to obtain MR images during an operation and use this information to achieve the maximal tumor resection, while at the same time, using the images to detect and avoid possible complications. To date, the scanner has been used in over thirty transsphenoidal pituitary procedures. When combined with the transnasal approach and endoscopy as needed, the scanner will facilitate maximal tumor resection while minimizing complications.

IMAGES BEFORE, DURING AND AFTER SURGERY ON A PITUITARY ADENOMA

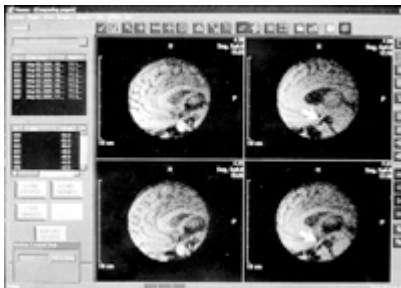


Figure 1. Intra-op MRI images pre- and post-resection of a nonfunctioning adenoma. The left two panels show pre-resection sagittal images obtained on the intra-op MRI without contrast; the



Figure 3a. This image shows a recurrent nonfunctioning macroadenoma as imaged by a 1.5T diagnostic quality machine.

right two panels show post-resection images - no visible tumor remains. The optic chiasm, not visible on the pre-op scans because of compression by the adenoma, is now visible on the post-op scans (arrow), and has been completely decompressed.

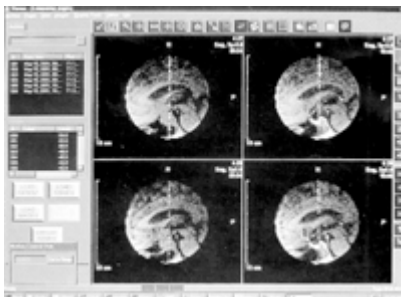


Figure 2. Intra-op MRI images showing pre- and post-resection views of a Rathke's cleft cyst in a patient whose initial presentation was for severe headaches. The left two panels show the cyst as a high signal mass within the sella; the right two panels show the cyst has been successfully drained. The patient's headaches resolved.

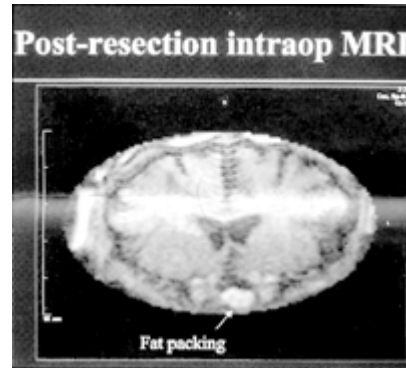


Figure 3b. After resection, an intra-operative image is obtained on the 0.12T portable machine. The tumor has been resected; the fat packing within the sella is bright.



Figure 3c. For comparison, a post-operative 1.5T image was obtained. The fat is suppressed (dark signal). No residual tumor was seen, confirming the intraoperative MRI finding of a complete resection of the lesion.

Journal Club

Topics in Growth Hormone Deficiency

by Beverly M.K. Biller, M.D.

Two recent Journal of Clinical Endocrinology and Metabolism articles address topics of interest related to adult growth hormone deficiency. The first report, entitled "Additional Beneficial Effects of Alendronate in Growth Hormone (GH)-Deficient Adults with Osteoporosis Receiving Long-Term Recombinant Human GH Therapy: A Randomized Controlled Trial", was conducted in the Netherlands by N. R. Biermasz et al. (1). These investigators designed a randomized, controlled trial in osteoporotic GH- deficient patients to

determine whether adding a bisphosphonate to stable growth hormone replacement would improve bone mass further.

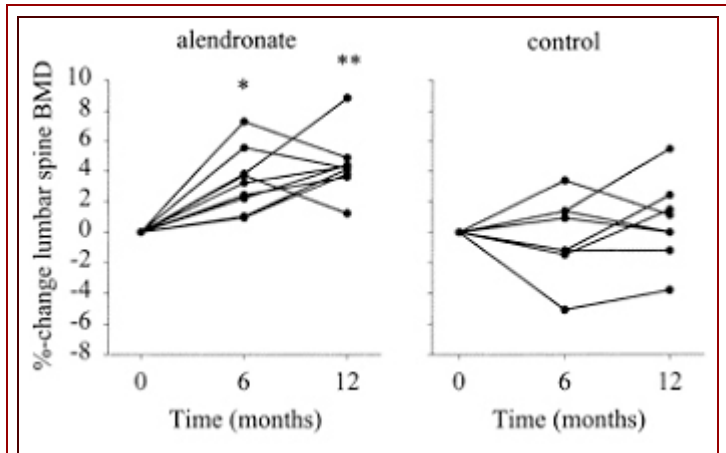
Eighteen patients were selected from a cohort of GH-deficient adults because of osteoporosis, defined as T score < -2 at the femoral neck and the lumbar spine. These subjects had already been receiving four years of GH replacement therapy. As one would anticipate, from the studies of long-term growth hormone replacement in GH-deficient adults, there had been a continuous increase in lumbar spine bone mineral density (BMD) prior to entry in the study, over the preceding four years of growth hormone replacement therapy, averaging approximately 1% per year. All patients were replete in vitamin D and calcium, had no disorders expected to affect BMD, and were on stable sex hormone replacement therapy for at least two years before entry into the study. All subjects had normal serum PTH concentrations, and none had been previously treated with bisphosphonates. The subjects were randomized to receive a daily dose of 10mg of alendronate or not, stratifying according to whether the GH deficiency was of adult or childhood onset. All patients maintained their GH replacement therapy at stable doses throughout the one-year study period. The primary endpoints in the study included: changes in biochemical markers of bone turnover, changes in bone mineral density measurements, and the incidence of new vertebral fractures.

The study showed a significant difference in biochemical markers of bone turnover between the two treatment groups. There were no significant changes in parameters of bone resorption (n-telopeptide) or bone formation (bone specific alkaline phosphatase and osteocalcin) during the study in the patients receiving growth hormone alone. In the patients receiving alendronate in addition to growth hormone, the urinary n-telopeptide/creatinine ratio decreased by 70.2±4% (p=0.002 for difference between groups). There was also a significant difference (p=0.001) between the decrease in serum bone specific alkaline phosphatase in the alendronate plus growth hormone-treated patients compared with that in the control patients receiving only growth hormone over the year of the study.

Measurement of bone mineral density showed that the patients receiving alendronate plus growth hormone had a 4.4% increase in lumbar spine BMD which was significantly (p=0.006) greater than the minimal change (0.7 percent) in the patients continuing to receive growth hormone as shown in the Figure. No new fractures developed in either group during the 12 month study period.

This study is interesting because it demonstrates that beyond the previously reported improvement in bone mass which can be achieved by replacing growth hormone in adult GH-deficient patients (2), the addition of alendronate to osteoporotic patients on stable GH therapy results in a further increase in bone mass. The authors appropriately point out that this study does not address the question as to whether bisphosphonate treatment alone would be beneficial in growth hormone deficient patients who were not taking GH replacement. This study was conducted in the Netherlands, where endocrinologists routinely supplement all growth hormone deficient patients with replacement. The authors indicate in the discussion that they would be unable to recruit a control population consisting of GH-deficient patients who were not receiving GH replacement. This observation reflects the high level of acceptance of growth hormone replacement in Europe compared with the United States. If confirmed in larger studies, these findings suggest that growth hormone deficient patients with severe osteopenia would likely benefit from the addition of alendronate to their growth hormone regimen.

The second article, entitled "Hypothalamo-Pituitary Surveillance Imaging in Hypopituitary Patients Receiving Long-Term Growth Hormone Replacement Therapy", by G. Frajese et al., from Saint Bartholomew's Hospital in London, addresses an important safety issue in GH replacement therapy (3). Some endocrinologists are concerned about the theoretical possibility that a sellar mass might enlarge with growth hormone replacement. It is important to recognize that there is an underlying recurrence rate of pituitary adenomas in patients who are not treated with GH of approximately 1% per year, depending on the series cited, and on the nature of the original tumor and the treatment which was administered. Therefore, it is to be expected that some patients treated with GH will have recurrent tumors. In order to link GH therapy as a causative agent in pituitary adenoma recurrence, a higher rate than expected must be demonstrated. This recent study is a prospective evaluation of serial head scans performed in 100



Individual percent change in lumbar spine BMD during the 12-month study period. The BMD increase was significantly greater at 6m in the alendronate plus GH group compared with the control group continuing on GH alone (, $P = 0.006$) and at 12 months (**, $P = 0.006$). (Biermasz et al, J Clin Endocrinol Metab, 2001; 86: 3083, Reproduced with permission from the Endocrine Society)*

consecutive patients initiated on growth hormone replacement for adult onset GH deficiency. The 60 females and 40 males who participated ranged in age from 18 to 69 years, and were confirmed to have GH deficiency on the basis of having a peak growth hormone response < 3 ng/ml following stimulation testing (insulin tolerance test in 81% of patients and glycogen stimulation test in 19% of patients). The most common diagnoses were clinically nonfunctioning pituitary adenomas, Cushing's disease, prolactinomas, and craniopharyngiomas. Ninety-one percent of patients had received radiation therapy in addition to surgery. Patients were treated between one and 32 years (median, 9 years) after the diagnosis of sellar abnormality. The dose of GH replacement was titrated to maintain serum IGF-I levels between the median and upper end of the age-related reference range.

Head scans (94% by MRI, 6% by CT due to claustrophobia or size) were performed at baseline, six months, 12 months, and annually thereafter in all subjects. Nearly all subjects (92%) were followed for at least two years and approximately one quarter of subjects had four years of follow-up. The study demonstrates that in 99% of patients, there was no increase in the amount of tissue within the pituitary fossa. Only one patient demonstrated growth of sellar tissue following initiation of growth hormone. This 40 year old man had been treated with surgery and radiation for a nonfunctioning pituitary adenoma three years prior to the initiation of GH. He had a partially empty sella on the baseline scan, and had expansion of sellar tissue to fill the pituitary fossa during the first six months of growth hormone therapy. The GH replacement was continued and no further change in sellar contents was observed.

These data are important because they show no increased risk of tumor recurrence beyond what is expected in patients with known pituitary disease. The authors were careful to point out in the discussion that most of their patients had received radiation therapy, at a rate higher than currently used in most pituitary centers, which may have affected the results. The authors also caution that because some of the patients had microprolactinomas or small corticotroph adenomas, the risk of recurrence in their population may have been lower than the expected rate. Certainly, the duration of the study (maximum follow-up four years) does not permit conclusions to be reached regarding the use of GH over a longer period of time. However, it has been established that children who were treated for GH deficiency as a result of CNS tumors (including malignancies) are at not increased risk for tumor recurrence as a result of GH replacement (4, 5). It will be important to continue to gather data regarding the risk of tumor enlargement in patients taking growth hormone replacement therapy. Nevertheless, to date, no published information

suggests that GH replacement confers any increased risk of tumor recurrence beyond what is expected from the natural history of treated pituitary adenomas.

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Growth Hormone Physiology and Treatment in HIV Disease

by Steven Grinspoon, M.D.

Recent data suggest that GH secretion is abnormal in HIV-infected patients. Increased GH concentrations during overnight frequent sampling are seen among patients with low weight and AIDS wasting (1). Conversely, reduced GH concentrations are seen in association with increased visceral adiposity among HIV-infected patients with the recently described fat redistribution syndrome in the setting of highly active antiretroviral therapy (2). It remains unclear whether HIV-infected patients with severe visceral adiposity are GH deficient, but recombinant human GH (rhGH) is now under investigation as a lipolytic agent in such patients. The spectrum of abnormalities in GH secretion in HIV disease and the potential therapeutic uses and limitations of rhGH in HIV disease will be reviewed in this article.

GH secretion is under the dual influences of somatostatin (inhibitory) and GHRH (stimulatory) and is nutritionally regulated. Acquired resistance to the action of GH occurs in acute and chronic undernutrition. Circulating GH stimulates secretion of Insulin-Like Growth Factor-I (IGF-I) via the GH receptor in the liver. In undernutrition, acquired resistance to the action of GH occurs by receptor and post-receptor mechanisms, resulting in reduced serum concentrations of IGF-I and increased GH. In prior studies, increased GH in association with reduced weight and lean body mass has been shown among men with the AIDS wasting syndrome (1, Figure 1).

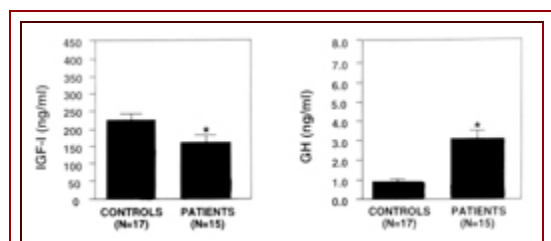


Figure 1. (Reproduced with permission from The Endocrine Society - Grinspoon, et.al.: *The Journal of Clinical Endocrinology & Metabolism*)

The wasting syndrome, defined as weight less than 90% IBW and/or weight loss > 10% of preillness baseline, is an AIDS defining complication of HIV disease and is a common manifestation of advanced HIV disease. Wasting occurs less often in the era of highly active antiretroviral therapy, but reduced muscle and lean mass are seen in up to 20% of patients treated with potent antiretroviral therapy.

1996;81:4051-8).

Growth hormone has been shown, at high doses (6 mg/day), to improve nitrogen balance and increase lean body mass in HIV-infected patients with the wasting syndrome (3). In a randomized, placebo controlled study, rhGH resulted in an improvement of approximately 3.0 kg in lean body mass as well as functional status (4). At the doses given, side effects including fluid retention and arthralgias were not uncommon. In contrast, standard replacement dosing for GH deficiency in adults with hypothalamic-pituitary disorders is much lower and initiated at doses as low as 0.002 mg/kg/day (equivalent to 0.14 mg/day in a 70 kg man). Given the physiologic resistance to GH in the AIDS wasting syndrome, it remains unknown if therapy with lower doses would be effective and better tolerated. The use of supraphysiologic dosing in AIDS wasting also contrasts to the potential uses of more physiologic dosing of GH in the HIV lipodystrophy syndrome (see below).

At the current time, patients experiencing wasting should be evaluated for malnutrition and malabsorption as well as hypogonadism. Treatment with testosterone in hypogonadal men with AIDS wasting has been shown to reduce GH secretion, as a function of improved lean body mass (5). Such experimental data suggests that testosterone, by improving lean body mass, reverses, in part, the acquired resistance to GH seen in the wasting syndrome. If no clear etiology exists for wasting in HIV-infected patients, treatment with rhGH may be considered in appropriate patients without known glucose intolerance or specific contraindications to rhGH.

In contrast, to the wasting syndrome, patients treated with highly active antiretroviral combination therapy often demonstrate abnormal accumulations of fat, particularly in the trunk and neck areas, in association with loss of subcutaneous fat in the extremities and face (6). Early estimates suggest that one half to three quarters of patients receiving highly active antiretroviral therapy experience changes in fat redistribution, known as the HIV lipodystrophy syndrome. The mechanisms of the HIV lipodystrophy syndrome are not known. In non HIV-infected patients, generalized obesity is associated with reduced GH secretion, which may be a function of increased somatostatin tone (7). Recent data suggest reduced GH concentration in HIV-infected patients with fat redistribution (2, Figure 2).

However, in contrast to the generalized obesity in non HIV-infected patients, GH concentrations were inversely related to excess abdominal visceral adiposity, but not BMI itself. These data suggest that reduced GH concentrations may be a function of the unique changes in body composition seen in HIV-infected patients. Such patients are unlikely to be GH deficient in the classical sense, but may have a functional deficiency in GH related to metabolic changes and

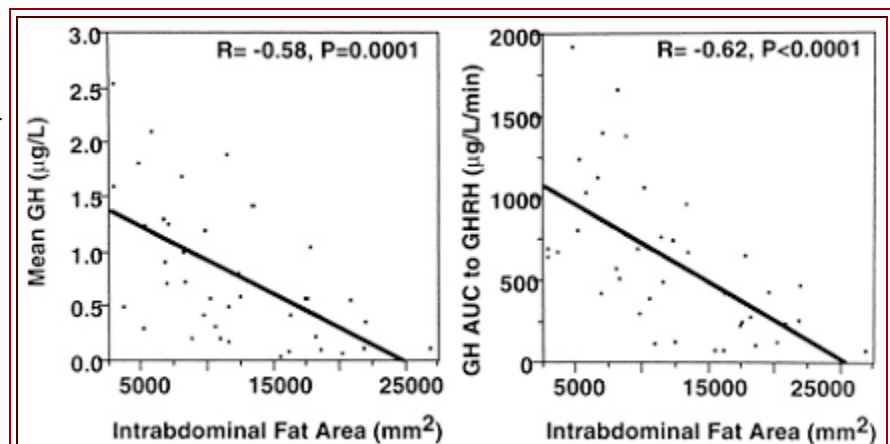


Figure 2. (Reproduced with permission from The Endocrine Society - Rietschel, et al: The Journal of Clinical Endocrinology & Metabolism 2001; 86:504-10).

increased visceral adiposity.

Growth hormone is lipolytic, and has recently been considered for treatment of the changes in fat redistribution associated with the lipodystrophy syndrome. Preliminary studies using supraphysiologic doses of growth hormone have resulted in a substantial reduction in visceral fat (8, 9). However, side effects, including worsening of glucose intolerance and symptoms of GH excess, have been associated with a dose of 6 mg/day. Further studies are now underway to determine if lower, more physiologic doses of GH may be useful to reduce excess visceral adiposity (10). It is possible that at sufficiently low doses of GH, lipolytic effects resulting in improved insulin sensitivity may outweigh direct negative effects of GH on insulin sensitivity. Recombinant human GH is not FDA approved for, and cannot be recommended for treatment of the HIV lipodystrophy syndrome until further data become available.

HIV disease is associated with a wide spectrum of abnormalities in GH secretion, including increased GH secretion in the wasting syndrome and reduced GH secretion in the lipodystrophy syndrome. Short-term recombinant human GH has been used successfully at supraphysiologic doses to increase lean body mass in patients with AIDS wasting. Studies are currently underway to determine the effects of lower doses of GH to reduce visceral adiposity in the HIV lipodystrophy syndrome.

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