



NEUROENDOCRINE CLINICAL CENTER BULLETIN

Winter 2009 Volume 16 / No. 2

Growth Hormone Therapy in Childhood Cancer Survivors:

Risk of Cancer Recurrence and Development of Secondary Neoplasm

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Recent decades have seen substantial improvements in childhood cancer therapies leading to increased survival rates, such that one in 900 young adults is a survivor of childhood cancer (1). As a result, late complications of these therapies are becoming more prevalent in both the adolescent and adult patient populations. Endocrine disorders resulting from hypothalamic-pituitary axis dysfunction are one of the most frequent late complications of these therapies, with growth hormone deficiency (GHD) being the most common. However, the mitogenic and proliferative properties of GH have prompted concern regarding the safety of administering GH replacement therapy to these deficient patients. There are many known consequences of GHD in both children and adults; however, studies evaluating cancer recurrence risk and the development of a secondary neoplasm after GH treatment have shown variable results.

The most common presentation of GHD in children is impaired linear growth evidenced by decreased growth velocity. Survivors who are GH deficient prior to completion of linear growth will often have short final adult height. In addition, GH plays an important role in the accrual of peak bone mineral density when entering adulthood (2, 3). Other symptoms of GHD in adults include diminished muscle mass and increased fat mass (4-7), abnormal lipid profiles (8), decreased bone mineral density

| Table 1 Risk of cancer recurrence and secondary neoplasm (SN) in children treated with GH replacement | | | | |
|---|------------------|--|---|--|
| Study | # Total patients | Recurrence | Secondary neoplasm | Study Conclusion |
| Moshang, et al., 1996 (51) | 1,262 | GH: 6.6% overall brain tumor recurrence | Not evaluated | GH therapy does not increase brain tumor recurrence |
| Swerdlow, et al., 2000 (52) | 1,071 | GH: 35 of 180 (19.4%) No GH: 437 of 891 (49%) | Not evaluated | GH therapy does not increase brain tumor recurrence |
| Packer, et al., 2001 (55) | 545 | GH: 40 of 170 (23.9%) | Not evaluated | GH therapy does not increase risk of medulloblastoma relapse or progression |
| Sklar, et al., 2002 (20) | 12,963 | GH: 6 of 361 (1.7%) No GH: 502 of 12,293 (4%) | GH: 15 of 354 (4.2%) No GH: 344 of 12,868 (2.7%) | GH therapy does not increase risk of cancer recurrence or development of secondary leukemia, but it does have a 3-fold increased risk of developing SN |
| Ergun-Longmire, et al., 2006 (47) | 14,108 | Not evaluated | GH: 20 of 361 (5.5%) No GH: 555 of 13,747 (4.0%) | Increased risk of SN following GH treatment appears to diminish with length of follow-up |
| Darendellier, et al., 2006 (54) | 2,503 | GH: 213 of 2,503 (8.5%) | Not evaluated | GH therapy does not increase brain tumor recurrence, GH dose did not differ between those with or without recurrence |
| Karavitaki, et al., 2006 (53) | 85 | GH: 4 of 32 (12.5%) No GH: 22 of 53 (41.5%) | Not evaluated | GH therapy is not a predictor of cranio-pharyngioma recurrence |

(9, 10), and diminished sense of well being (11-13). In addition, GH deficient individuals have been shown to have increased risk of cardiovascular disease (14) and increased inflammatory cardiovascular risk markers (15). All of these possible complications of GHD illustrate the importance of evaluating GH status of individuals at risk.

GHD may result from anatomic defects associated with primary or metastatic tumors near the hypothalamic-pituitary region or from the treatment of other central nervous system (CNS) tumors (16). In

addition, CNS radiation, including radiation therapy for leukemia or prior to bone marrow transplant, may result in pituitary hormone deficiencies, particularly GHD (17). Animal studies have shown a marked sensitivity of the GH-producing somatotroph cells to radiation doses as low as 300 cGy (18). In addition, variable degrees of GHD may result from dual damage to both the pituitary and hypothalamus (19). The risk of GHD after cranial irradiation is increased in younger patients (20) and in

continued on page 2

patients receiving higher total and fractionated doses of radiation (21). Doses greater than 24 Gy result in GHD in up to two-thirds of patients (21-26) but doses as low as 10 Gy can cause GHD in young children (22, 27, 28). Cranial radiation greater than 30 Gy is associated with a 10 year post-radiation risk of GHD in more than 80 percent of patients (24). Chemotherapy alone may lead to GHD but at a much lower rate than that of radiotherapy (29).

GH is known to have mitogenic and proliferative effects on many tissues either directly or indirectly through the action of insulin like growth factor-1 (IGF-1). Studies have demonstrated the increased expression of GH receptors in human breast cancer cells (30), melanoma (31), and colorectal carcinoma (32). In addition, IGF-1 mRNA expression has been found to be increased in tumor cells of many types of cancers when compared to normal cells, including glioblastoma, astrocytoma (33), meningioma (34), colon carcinoma (35), pancreatic carcinoma (36), and breast cancer (37) cells among others. IGF-1 has been shown to stimulate thyroid cell growth and increased numbers of IGF-1 receptors have been found on malignant thyroid epithelial cells (38). These actions of GH and IGF-1 have prompted concerns that administering GH may stimulate tumor cell growth or proliferation and lead to cancer recurrence, development of secondary neoplasm, or leukemia.

The associations of leukemia with GH have been a source of some controversy. Data are conflicting with some studies describing an increased incidence of leukemia in children treated with GH (39, 40), whereas more recent studies have not been able to replicate these results (41, 42). In 1981, Mercola *et al.* demonstrated that

human lymphocytes have GH receptors and that the addition of GH to tissue culture stimulated the proliferation of normal T lymphocytes (43). Giesbert *et al.* evaluated 44 leukemic cell lines and found GH receptors in the cytoplasm of all cell lines but only some of the cells displayed GH receptors on the cell surface. Those cells with surface GH receptors did undergo a dose dependent increase in receptor number when incubated with GH. However, GH stimulated cell proliferation only occurred in three of the 13 leukemic cell lines (44). Estrov *et al.* obtained leukemic cells from bone marrow aspirates and evaluated the effects of both GH and IGF-1 on cell proliferation. They found that cell proliferation did occur but only in the presence of phytohemagglutinin-stimulated T-cell-conditioned medium, suggesting that the presence of GH receptor does not ensure that GH or IGF-1 will stimulate cell proliferation (45). To evaluate the incidence of leukemia in children with multiple causes of GHD, Allen *et al.* evaluated the National Cooperative Growth Study database with 24,417 children who had received recombinant GH between November 1985 and December 1995. A total of eleven new cases of leukemia were diagnosed, however eight of these were found in patients who had risk factors for leukemia including various genetic conditions and previous tumors or radiation (41). Another important study by Rappaport *et al.* described four patients with primary CNS tumors who were treated with radiation and developed GHD. These patients did not receive GH therapy and still developed a secondary leukemia suggesting that radiation rather than GH may lead to the development of leukemia (46).

Studies evaluating the risk of cancer

recurrence and the development of a secondary neoplasm have also shown variable results. Sklar *et al.* evaluated 13,539 patients in the Childhood Cancer Survivor Study, a cohort of five year survivors of childhood cancer. There were 361 patients who received GH therapy. Six patients receiving GH therapy experienced a recurrence of primary cancer. All of these cancer survivors had also received radiation of the face or brain. Recurrences were described in 502 patients who did not receive GH therapy. The authors adjusted for age at diagnosis, radiation, and chemotherapy effects with a time-dependent Cox model and found a relative risk of 0.83 (95% confidence interval, 0.37-1.86; P=0.65) for recurrence in GH-treated survivors when compared with patients not treated with GH. Thus, GH-treated patients were not found to have an increased risk of developing primary cancer recurrence. Complete information regarding secondary neoplasms was available for 13,222 patients in this cohort, of which 354 had been treated with GH. Fifteen GH-treated patients developed a secondary neoplasm compared to 344 of the non-GH treated patients. Thirteen of the GH-treated patients developed the secondary neoplasm at a site previously exposed to radiation. After adjusting for age at diagnosis, sex, radiation, and alkylating agents, the relative risk of developing a secondary neoplasm after GH therapy was 3.21 (95% confidence interval 1.88-5.46; P<0.0001) when compared to patients not receiving GH. This overall increased risk appears to be driven in part by the higher number of secondary neoplasms developing in primary acute leukemia survivors (relative risk 4.98). It is also important to note that all 15 secondary neoplasms were solid tumors

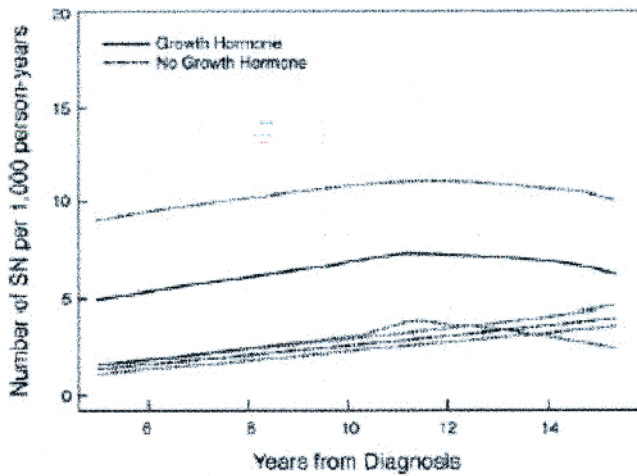
Table 2 Recurrence of brain tumors in patients treated with growth hormone from KIGS study

| Tumour characteristics | n | Age at tumour diagnosis (y) | Age at onset of GH therapy (y) | Dose at GH start (mg/kg/wk) | Surgery, n (%) | Surgery + radiotherapy, n (%) | Surgery + radiotherapy + chemotherapy, n (%) | |
|------------------------|--------------------|-----------------------------|--------------------------------|------------------------------|------------------|-------------------------------|--|------------|
| Astrocytoma-glioma | Without recurrence | 361 | 8.5 (3.2-13.4) p = 0.021 | 10.2 (6.4-14.1) p < 0.001 | 0.18 (0.10-0.26) | 44 (16.9) | 156 (60.0) | 60 (23.1) |
| | With recurrence | 39 | 7.0 (1.8-10.4) | 8.0 (4.1-13.1) | 0.17 (0.12-0.24) | 6 (20.0) | 17 (56.7) | 7 (23.3) |
| Craniopharyngioma | Without recurrence | 917 | 9.8 (4.3-14.9) p < 0.001 | 10.7 (5.3-15.4) p < 0.000 | 0.17 (0.10-0.25) | 507 (62.2) | 290 (35.6) | 18 (2.2) |
| | With recurrence | 121 | 8.4 (3.2-13.2) | 8.9 (3.4-13.6) | 0.17 (0.11-0.25) | 79 (79.0) | 20 (20.0) | 1 (1.0) |
| Ependymoma | Without recurrence | 103 | 7.6 (2.1-12.7) | 9.7 (6.4-13.6) | 0.19 (0.13-0.27) | 1 (1.0) | 43 (43.9) | 54 (55.1) |
| | With recurrence | 10 | 7.6 (1.9-9.8) | 9.0 (5.1-12.5) | 0.20 (0.16-0.27) | 3 (33.3) | 6 (66.7) | 6 (66.7) |
| Germinoma | Without recurrence | 285 | 12.1 (7.9-15.4) | 12.6 (9.3-16.0) | 0.16(0.11-0.26) | 9 (4.9) | 89 (48.4) | 86 (46.7) |
| | With recurrence | 12 | 11.8 (6.3-13.8) | 12.3 (9.8-13.8) | 0.18 (0.11-0.24) | 2 (50.0) | 2 (50.0) | 2 (50.0) |
| Medulloblastoma | Without recurrence | 624 | 8.5 (3.8-12.8) p < 0.0001 | 10.1 (6.3-14.0) p = 0.004 | 0.20 (0.14-0.29) | 7 (1.3) | 179 (32.1) | 372 (66.7) |
| | With recurrence | 31 | 10.8 (6.8-14.0) | 11.2 (9.1-15.2) | 0.21 (0.14-0.31) | 5 (17.9) | 23 (82.1) | 23 (82.1) |

Values are given as medians, with the 10th-90th percentile values shown in parentheses.

From Darendellier, et al. Recurrence of brain tumours in patients treated with growth hormone: Analysis of KIGS (Pfizer International Growth Database). Acta Paediatrica. 2006; 95:1284-90. Reproduced with permission from Blackwell Publishing Ltd.

Figure 1



Comparison of the number of SN estimated per 1000 person-years for survivors who did and did not receive treatment with GH, plotted against time from diagnosis. The plot includes 95% CIs.

From Ergun-Longmire B et al. 2006. Growth Hormone Treatment and Risk of Second Neoplasms in the Childhood Cancer Survivor. *J Clin Endocrinol Metab.* 91:3494-8. Copyright 2006, The Endocrine Society.

and none of these patients developed secondary leukemias (20). Although several similar studies have been done, the large number of patients evaluated in this study should not be overlooked.

A follow-up study of patients in the Childhood Cancer Survivor Study by Ergun-Longmire *et al.* (47), found that although GH-treated survivors appear to have an increased risk of developing a secondary neoplasm, the elevation in risk diminishes with increasing length of follow-up. Data for this retrospective evaluation were obtained 32 months after the initial evaluation by Sklar *et al.* During this follow-up analysis, 14,108 survivors were eligible for evaluation. Twenty cases of secondary neoplasm were found in the 361 patients who received GH (five new cases in addition to the initial 15 patients described by Sklar *et al.*) and all of these patients had also received radiation. Secondary neoplasms were detected in 555 of the 13,747 survivors who were not treated with GH (211 in addition to the initial 344 patients described by Sklar *et al.*) (Figure 1). After adjusting for potential confounders including age at diagnosis, sex, radiation, and alkylating agent effects, the rate ratio of secondary neoplasms in GH-treated survivors was 2.15 (95% confidence interval 1.33-3.47; $P=0.002$). Of note, nine of the 20 secondary neoplasms in the GH-treated group were meningiomas and all nine patients received cranial radiation (47). Meningiomas have been shown to develop after cranial radiation in both benign and malignant conditions (48-50). Also in this study, Ergun-Longmire *et al.* found no reports of secondary leukemia (47).

Multiple studies have specifically evaluated the effects of GH treatment in survivors of childhood brain tumors. The National Cooperative Growth Study (NCGS) evaluated 19,000 patients treated with GH replacement therapy including

1,262 brain tumor survivors. This study found that the overall tumor recurrence rate in these patients was 6.6%. The individual recurrence rates for specific tumor types were 6.4% for craniopharyngioma, 7.2% for primitive neuroectodermal tumor, and 20% for glioma (51). The authors concluded that recurrence rates were not significantly different between the GH-treated patients in their study and established recurrence rates for non-GH treated patients. This study did not include data on age at diagnosis, radiation therapies, or surveillance after discontinuation of GH therapy.

A study from the United Kingdom by Swerdlow *et al.* also concluded that GH treatment following radiotherapy for childhood brain tumors does not increase the risk of primary tumor recurrence. These investigators retrospectively evaluated 1,071 survivors of childhood brain tumors who had all received radiotherapy. Patients with craniopharyngiomas were not included in this group of patients. The authors found a recurrence of primary brain tumors in 35 of the 180 GH-treated patients (19.4%) versus 437 of the 891 patients not treated with GH (49%). After adjusting for age at diagnosis and tumor histology, the overall relative risk was 0.6 (95% confidence interval 0.4-0.9; $p<0.05$), thus indicating that GH-treated patients were not at increased risk for brain tumor recurrence (52). These authors did point out that although their results may appear to suggest that those patients who were treated with GH had a lower rate of recurrence, caution should be used when interpreting their results in this way. Karavitaki *et al.* specifically evaluated the recurrence risk of craniopharyngioma in 85 patients over a 40 year period. There were 32 patients treated with GH and 53 non-treated patients. Four GH-treated patients (12.5%) developed a tumor recurrence. Two patients had partial

resections of the initial tumor and two had surgical excision plus radiotherapy. Twenty-two non-GH treated patients (41.5%) developed a recurrence. Eighteen of these patients had partial resection and four had surgical excision plus radiotherapy (53).

Darendeliler *et al.* (54) analyzed the Pfizer International Growth Database (KIGS) to evaluate the recurrence risk of brain tumors in survivors treated with GH compared to published reports of tumor recurrence in non-GH treated patients. They evaluated 2,503 patients in the database and found that 213 had tumor recurrence and that the overall incidence did not differ from non-GH treated patients in other published reports. GH dose was also evaluated and did not significantly differ between the GH-treated patients with or without tumor recurrence. Recurrence rates did vary with different types of initial treatments as shown in Table 2 (54).

Five hundred forty-five patients with medulloblastoma from eleven neuro-oncology centers were retrospectively evaluated by Packer *et al.* to determine the effects of GH therapy on tumor relapse. All patients were 15 years old or younger at tumor diagnosis and 170 were treated with GH replacement therapy. The authors found no statistical evidence of association between the use of GH and progression-free survival in either infants (relative risk 0.710 with 95% confidence interval 0.648-4.267, $P=0.71$) or older children (relative risk 0.648 with 95% confidence interval 0.365-1.150, $P=0.138$). Although this study had an impressive number of 545 survivors of medulloblastoma, it is important to note that GH treatment criteria varied widely between the eleven different institutions and may have influenced the results (55).

Important considerations in the interpretation of these studies are the potential selection bias and multiple unknown con-

founders. Patients with more aggressive cancers often require more extensive treatment which may lead to increased deleterious effects on the hypothalamic-pituitary axis. These patients are not only at an increased risk for the development of hormonal deficiencies but also the detrimental effects of the chemotherapy and/or radiation used in their treatment. In addition, unknown genetic factors leading to predispositions for the development of cancer may increase the risk for some patients to develop secondary cancers regardless of the administration of GH. Also, some of the data in these studies was collected prior to the routine use of recombinant human GH (rhGH). Of the studies discussed here, only two verified that all of their subjects received rhGH (51, 54).

Although data regarding the use of GH therapy in cancer survivors with GH deficiency are conflicting, several studies have now shown that the risk of tumor recurrence is not elevated compared to non-GH treated survivors. In addition, the potential elevated risk of a secondary neoplasm following GH therapy appears to diminish with increased length of follow-up. This suggests the possibility that those patients who are predisposed to develop a secondary neoplasm will do so earlier but do not necessarily have an overall increased risk secondary to the administration of GH. Additional studies are needed; however, this medical problem is complicated by the difficulty in obtaining randomized controlled trials to control for multiple known and unknown confounders. In conclusion, the benefit of GH therapy in GH deficient childhood cancer survivors may outweigh the risks but patients should still undergo frequent screening for the development of recurrence or a secondary neoplasm.

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Growth Hormone Deficiency after Definitive Therapy for Acromegaly: Part I - Quality of Life

Karen K. Miller, MD

Growth hormone deficiency (GHD) commonly develops after treatment of pituitary tumors in adults and is complicated by many clinical sequelae, including impairment of quality of life (1-4). Moreover, randomized, placebo-controlled studies have demonstrated that growth hormone replacement therapy reverses many of the deleterious effects of GHD, including on quality of life (5-9). Studies have also shown that patients at the other end of the GH spectrum — those with growth hormone (GH) excess due to GH-secreting pituitary tumors (acromegaly) — also experience a diminished quality of life (4, 10-14). To further complicate matters, such patients may develop GH deficiency after definitive treatment (surgery and/or radiation therapy) for their acromegaly. Studies have demonstrated a 30 to 50% percent risk of GHD in patients treated for acromegaly with conventional radiotherapy (15-17). A recent study demonstrated a 61% incidence of GHD in patients after definitive treatment for acromegaly, including 71% in patients who received surgery followed by conventional radiation therapy (18). Interestingly, a 55% incidence of severe GHD was reported in patients treated with surgery alone (i.e. in patients without any history of radiation whatsoever) (18). These data raise the question of whether patients who have developed GHD after definitive treatment of acromegaly experience impaired quality of life compared with patients who have normal GH levels after cure of acromegaly

and, if they do, whether they would benefit from GH replacement therapy.

To address the first question, we compared quality of life measures in 27 patients with GHD following cure of acromegaly with those of 19 patients with normal GH levels (“GH sufficiency”) after treatment of acromegaly (19). GH deficiency was defined as a peak GH level of less than 5 ng/ml on stimulation (with GHRH-arginine or on an insulin tolerance test) or a low IGF-1 level in the presence of at least three pituitary hormone deficiencies.

Three validated quality-of-life questionnaires were administered, as follows: 1) Quality of Life Adult Growth Hormone Deficiency Assessment (QoL-AGHDA), 2) Short-Form Health Survey (SF-36) and 3) The Symptom Questionnaire. The results are shown in Figures 1 and 2 and demonstrate significant impairment of quality of life on nearly all subscales in the GH-deficient compared with GH-sufficient study participants, all of whom previously had acromegaly (19). This included a higher mean score on the QoL-AGHDA, a questionnaire developed as an integrated measure of impaired quality of life in domains particularly affected by GHD. It also included decreased energy (“Vitality”) on the SF-36, a questionnaire widely used to detect impaired quality of life in patients with medical conditions, and increased depressive and somatic symptoms on the Symptom Questionnaire. Of note, the mean scores of four out of eight subscales on the SF-36 questionnaire were below

normal in the GH-deficient group, whereas mean scores for the GH-sufficient group were all well within the normal range (19).

The degree of impairment we observed for patients with GHD after cure of acromegaly was similar to that published for patients with GHD after treatment of non-somatotroph tumors (1, 20-22), and was comparable to that of patients with type II diabetes mellitus or recent

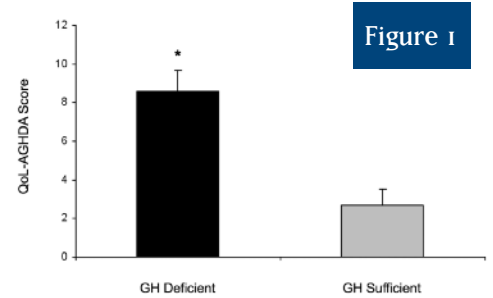


Figure 1. Mean (± SEM) AGHDA scores were higher in the GH-deficient than GH-sufficient subjects with prior acromegaly. Black bar, GH-deficient; grey bar, GH-sufficient. *, $p=0.0002$. Higher scores on the AGHDA indicate poorer quality of life.

From Wexler T, et al. 2009. Growth Hormone Deficiency Is Associated with Decreased Quality of Life in Patients with Prior Acromegaly. *J Clin Endocrinol Metab.* 94(7):2471-7. Copyright 2009, The Endocrine Society.

acute myocardial infarction. The degree of quality of life impairment was greater than in subjects with hypertension and other minor medical conditions (23, 24). This suggests that the severity of impairment of quality of life observed in our study is clinically important.

These data raise two important questions. First, would GH replacement therapy improve quality of life and/or other abnormalities, such as increased visceral adiposity, in patients with GHD but a history of acromegaly, as has been established in patients who develop GHD after treatment of other types of tumors? Moreover, is GH replacement therapy well-tolerated in such patients? Stay tuned — these questions will be addressed in a future Neuroendocrine Clinical Center Bulletin.

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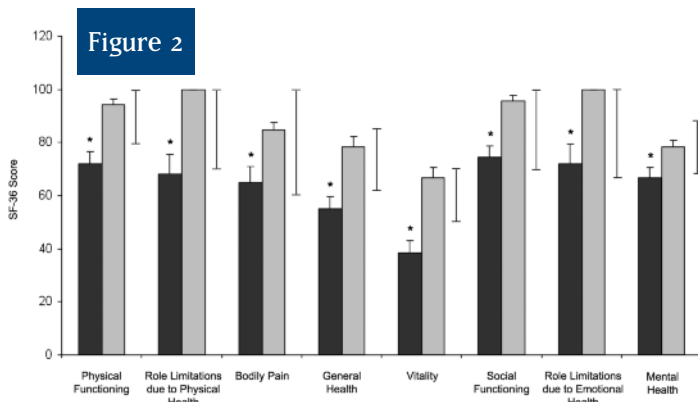


Figure 2. Mean SF-36 (± SEM) scores were lower for all subscales in the GH-deficient than GH-sufficient subjects with prior acromegaly. Black bar, GH-deficient; grey bar, GH-sufficient; bracket, normal ranges. *, $p<0.03$. Lower scores on the SF-36 questionnaire indicate poorer quality of life.

From Wexler T, et al. 2009. Growth Hormone Deficiency Is Associated with Decreased Quality of Life in Patients with Prior Acromegaly. *J Clin Endocrinol Metab.* 94(7):2471-7. Copyright 2009, The Endocrine Society.

Neuroendocrine Unit News Impacting Pituitary Patient Care and Research

Two major events impacting patients with pituitary conditions were held here in 2009. The first, a day devoted to the education of patients with the rare condition of Cushing's disease, was attended by patients and families. The second occasion celebrated the establishment of an endowed chair that will enable further research in acromegaly and other neuroendocrine disorders.

Cushing's Disease Patient Education Day

On Saturday, February 28, 2009, the Cushing's Support and Research Foundation (CSRF) hosted the first Patient Education day. About 120 patients with Cushing's disease, many accompanied by family and friends, attended the day-long event at the Boston Intercontinental Hotel.

Nine MGH Neuroendocrine Clinical Center members, Dr. Karen K. Miller, Dr. Beverly M.K. Biller, Dr. Anne Klibanski, Dr. Lisa Nachtigall, Dr. Brooke Swearingen, Dr. Elena Valassi, Dr. Madhu Misra, Michelle Gurel, BSN, R.N. and Karen J.P. Liebert, BSN, R.N., and speakers from other institutions donated their time to teach the attendees. Topics included normal pituitary gland function and the clinical features, diagnosis, testing paradigms and treatment of Cushing's syndrome in adults and children. One highlight of the day was a video of a transsphenoidal operation narrated by the MGH expert pituitary neurosurgeon, Dr. Brooke Swearingen. Other highlights included a talk by nurse Michelle Gurel who spoke about what patients could expect prior to and after transsphenoidal surgery and a panel of patients who shared their experiences with the audience. Said one attendee, "Aside from the wealth of information you provided to all of us, you also provided a forum where we all could finally feel we were amongst others who understood exactly what we'd been through".

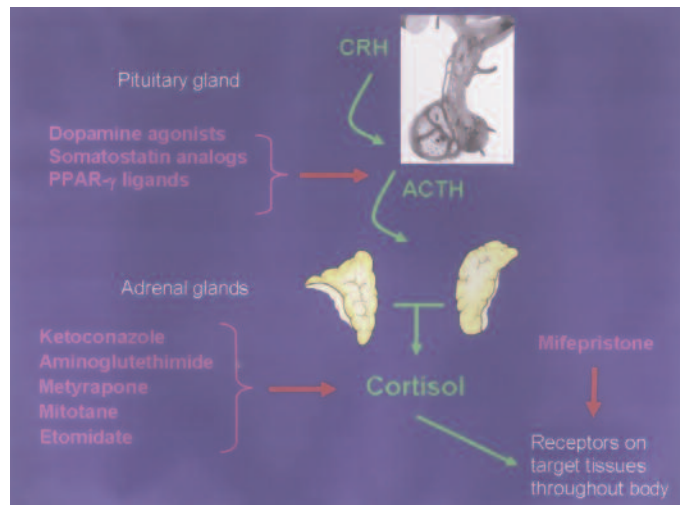
Louise Pace, CSRF Founding President and Karen Campbell, Director of CSRF organized the event, which was free for attendees. According to Ms. Pace, "This day is truly a milestone. We all know how important it is to have excellent information about Cushing's." Further information, including details about the information packets assembled by Neuroendocrine Clinical Center nurses Karen JP Liebert and Michelle Gurel for patients at the event, can be found on the CSRF website at:

http://www.csrf.net/page/cushings_patient_education_day.php

Celebration of the Laurie Carrol Guthart Professorship in Medicine in the Field of Neuroendocrinology

On May 29, 2009 in a formal ceremony at Harvard Medical School (HMS), Dr. Anne Klibanski, Chief of the MGH Neuroendocrine Unit, was honored as the first incumbent of the Laurie Carrol Guthart Professorship in Medicine in the Field of Neuroendocrinology at HMS.

The chair was established in 2008 by Leo A. Guthart, MBA, DBA, his family, daughters Rebecca Guthart and Margaret Guthart Strauss, and his son-in-law, Edward Strauss in honor of Dr. Guthart's late wife Laurie to advance research in Neuroendocrine disorders. Mr. Guthart provided a moving history



This figure, demonstrating the sites of action of available and investigational medications being used and/or studied in the treatment of Cushing's, was shown at the CSRF Patient Educational Day.



Faculty at the Cushing's Disease Patient Education Day. Left to right; Beverly M.K. Biller, MD, Anne Klibanski, MD, Lisa Nachtigall, MD, Brooke Swearingen, MD, Michelle Gurel, BSN, RN

Reception for the Laurie Carrol Guthart Professorship in Medicine in the field of Neuroendocrinology. Left to right; Anne Klibanski, MD, Roy Soberman, MD, Leo Guthart, MBA, DBA



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 preoperative medical treatments | Karen Pulaski-Liebert, R.N. Dr. Beverly M.K. Biller |
| Cushing's Syndrome | •Evaluating a potential new medical therapy | Karen Pulaski-Liebert, R.N. Dr. Beverly M.K. Biller |
| Adolescent athletes | •Investigating impact of hormonal alterations on menstrual function and bone density | Dr. Madhu Misra Dr. Anne Klibanski |
| Adolescent boys and girls with depressive disorders | •Investigating impact of hormonal alterations on reproductive function and bone density | Dr. Madhu Misra Dr. Anne Klibanski |
| Women with anorexia nervosa | •New therapies | Dr. Karen K. Miller Dr. Anne Klibanski |
| Women ages 18-25 with a history of anorexia nervosa | •Investigating hormones and brain circuitry involved in appetite | Dr. Elizabeth Lawson Dr. Anne Klibanski |
| Obese women ages 18-25 | •Investigating hormones and brain circuitry involved in appetite | Dr. Elizabeth Lawson Dr. Anne Klibanski |
| Obese men, ages 18-45 | •Investigating the effects of GH administration on 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 |
| Healthy men and women, normal weight and obese | •Short-term GHRH | Dr. Takara Stanley Dr. Steven Grinspoon |
| Overweight children | •Effects of exercise on mitochondrial function | Dr. Amy Fleischman Dr. Steven Grinspoon |
| HIV positive men and women with 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 |

of his interest in the field: “Laurie, who was the daughter of an internist who practiced medicine actively for 58 years, also read extensively and immersed herself in learning everything she possibly could about pituitary tumors. She and I both decided that getting involved in the Neuroendocrine Clinic’s research program would be meaningful for our family and could do some real good so we asked Anne [Klibanski] what projects she was involved with. I got really excited about the program when Anne explained to me that she was using Representational Differential Analysis, known as RDA, to try to determine the genetic pathways leading to pituitary tumors. I had done some work at Cold Spring Harbor Laboratory with Mike Wigler, who developed RDA, in applying it to breast cancer. RDA compares normal tissue with tumor tissue in the same individual in an attempt to pinpoint the genomic difference of the tumor. Once I understood what Anne was doing, I became an active and enthusiastic supporter of her research work and Laurie gave her full encouragement and support.”

Both the current Dean of HMS, Jeffrey Flier, MD, as well his predecessor, Dean Joseph Martin, an early mentor of Dr. Klibanski, were in attendance, as were the MGH Chief of Medicine Dr. Dennis Ausiello, MGH President Peter L. Slavin, and over 200 colleagues and trainees who have worked with Dr. Klibanski.

Dr. Klibanski noted, “This chair will enable continued leadership of the MGH in research, clinical care and training in neuroendocrinology and pituitary disorders.” She noted the multidisciplinary nature of the field and emphasized that the establishment of this chair highlights the importance of advancing both basic and clinical research in pituitary disorders, which will ultimately improve patient care.

Endocrinology:

Anne Klibanski, MD
Chief, Neuroendocrine Unit
 Beverly M.K. Biller, MD
 Steven K. Grinspoon, MD
 Elizabeth A. Lawson, MD
 Hideo Makimura, MD, PhD
 Janet Lo, MD
 Karen K. Miller, MD
 Lisa B. Nachtigall, MD
 Melissa K. Thomas, MD, PhD
 Nicholas A. Tritos, MD, DSC

Neurology:

Thomas N. Byrne, MD

Neurosurgery:

Robert L. Martuza, MD
Chief, Neurosurgical Service
 Brooke Swearingen, MD
 Nicholas T. Zervas, MD

Radiation Oncology:

Jay S. Loeffler, MD
Chief, Radiation Oncology
 Helen A. Shih, MD

Psychiatry:

George Papakostas, MD

Pediatric Endocrinology

Madhusmita Misra, MD, MPH

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' 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.

In 2009, the MGH Neuroendocrine Clinical Center Bulletin was supported in part by unrestricted educational grants from: Corcept and LG Life Sciences. Dr. Biller, Editor of the Neuroendocrine Clinical Center Bulletin, has served as consultant for LG Life Sciences and is the primary investigator on a research grant to the Neuroendocrine Unit from Corcept.



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