



## Neuroendocrine & Pituitary Tumor Clinical Center (NEPTCC) Bulletin

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### Understanding Growth Hormone Deficiency in HIV Lipodystrophy

SUMAN SRINIVASA, MD

Perturbations in the growth hormone (GH) axis are common among the well-treated human immunodeficiency virus (HIV)-infected population [1]. Acquired GH deficiency (GHD) secondary to HIV is a clinical diagnosis in the absence of known pituitary or hypothalamic pathology and should be differentiated from idiopathic adult GHD. Studies have determined that a GH peak cutoff of 7.5 ng/mL during the GHRH-arginine test can adequately discriminate GHD in HIV-infected individuals compared to healthy individuals with good specificity. As much as a third of HIV-infected individuals are estimated to have an inappropriate response to GHRH-arginine stimulation testing [2].

A spectrum of disease from true GHD to GH insufficiency exists among the HIV population. Recent studies have reported that the severity of GHD is far greater in the setting of pituitary disease compared to HIV infection [3], as measured by peak GH and area under the curve GH during GHRH-arginine testing. When an abnormally low IGF-1 is detected, it may be prudent to formally rule out pituitary insufficiencies and determine whether pituitary imaging is warranted; however, in most scenarios, the GHD may likely be ascribed to a known history of HIV.

Normal GH levels play an important role in the maintenance of body composition. In this regard, GHD is associated with accumulation of visceral fat and loss of lean body mass. The visceral fat depot is associated with increased cardiometabolic mortality [4]. Studies demonstrate that HIV-infected individuals have increased visceral adipose tissue (VAT) accumulation when compared to non-HIV individuals [5] and are at risk for acquired lipodystrophy [6]. Several mediators have been implicated in VAT accumulation, including non-contemporary antiretroviral therapies, the HIV virus itself, chronic inflammation and immune activation, or perturbations in hormone systems, particularly the GH axis. Moreover, HIV-infected individuals are at risk for age-related disease, not limited to cardiovascular disease, and some have hypothesized that impairment in the GH axis could be related to a phenotype consistent with premature aging [3]. Indeed, studies in the non-HIV population have determined that GH replacement can play

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a significant role in improving metabolic outcomes, related to improvements in body composition, dyslipidemia, inflammation, cardiovascular and bone health [7-13], which could serve as an important treatment paradigm in HIV lipodystrophy.

Detailed physiology studies have been performed to characterize GH dynamics in HIV. Overnight frequent sampling among HIV-infected individuals with and without lipodystrophy and healthy individuals demonstrated that the HIV group with lipodystrophy had reduced basal and mean GH concentration, as well as GH pulse amplitude, while GH pulse frequency and IGF-1 levels were normal when compared to the HIV non-lipodystrophy and healthy control groups [14]. Visceral adipose tissue (VAT) accumulation was predictive of reduced GH in the HIV population.

The directionality and interrelationship between GHD and VAT accumulation in HIV remain largely unclear. That is, VAT accumulation, as seen in lipodystrophy, could attenuate GH secretion. Alternatively, GHD could lead to VAT accumulation, as is demonstrated in pituitary conditions resulting in GHD. Aside from VAT accumulation, other proposed mechanisms responsible for perturbations in GH dynamics in HIV include: altered ghrelin release, increased somatostatin tone, and suppressive effects of fatty free acids on GH [15].

Further studies have determined an effect of sex on GHD among the HIV population. Under formal GH stimulation testing, HIV-infected men have reduced peak GH in response to the GHRH-arginine stimulation test when compared to HIV-infected women matched for age, BMI, and race [16]. A sex-specific mechanism remains unclear. The differences in GH physiology could be attributed to endogenous estrogen, which is recognized to decrease IGF-1 and therefore reduce inhibitory feedback on GH. Other studies have proposed that fat redistribution is a key driver, such that an increased VAT to SAT ratio among HIV-infected men vs. HIV-infected women accounts for the observed differences in GH physiology [17].

Restoration of GH physiology could have the potential to decrease the risk of morbidity and mortality in HIV if there is visceral fat

## Understanding Growth Hormone Deficiency in HIV Lipodystrophy - Continued

reduction and reduced cardiometabolic risk. Overall, few treatment strategies exist to decrease cardiometabolic risk in HIV. Leveraging unique GH physiology in HIV, several studies have investigated the benefit of GH and growth hormone releasing hormone (GHRH) analogues to restore GH function among HIV-infected individuals.

A randomized controlled trial was conducted to assess the effects of low dose GH (average dose 0.33 mg/day) vs. placebo over 18 months on body composition and metabolic indices in a group of HIV-infected individuals with abdominal fat accumulation and reduced GH secretion (peak GH <7.5 ng/mL during the GHRH-arginine test). Results demonstrated a significant treatment effect of GH to reduce VAT area by -19cm<sup>2</sup> with preservation of the subcutaneous adipose tissue (SAT) area. However, the benefits to improved body composition might be outweighed by a significant worsening of 2 hour glucose levels on glucose tolerance (treatment effect of GH on glucose +22 mg/dL) [18]. Withdrawal of low dose GH among HIV-infected individuals was associated with reaccumulation of VAT [19]. There is relatively more VAT reduction with higher dose GH (2-4 mg/day), but this is accompanied by SAT reduction as well [20-22]. SAT reduction could be detrimental if there is clinical evidence of lipodystrophy, as SAT is a vital storage depot for triglycerides. Moreover, continued loss of fat in the limbs or face in HIV-associated lipodystrophy is not typically desired and can have negative effects on quality of life. GH treatment is currently not approved for use in HIV-associated lipodystrophy.

Newer studies have evaluated the use of a growth hormone releasing hormone (GHRH) analogue, tesamorelin, in HIV. Use of a GHRH analogue takes advantage of the fact that adequate endogenous pituitary reserve may be present among HIV-infected individuals, which can be augmented with an exogenous hypothalamic peptide. In addition, stimulating pulsatile GH secretion maintains the negative feedback system from IGF-1 signaling. Compared to GH, tesamorelin is thought to have neutral effects on glucose and therefore may avoid worsening insulin sensitivity.

The majority of studies evaluating tesamorelin have enrolled HIV-infected individuals regardless of their baseline GH status. Nonetheless, use of a GHRH analogue demonstrates good efficacy in reducing VAT. Data from a randomized controlled trial of over 400

HIV-infected individuals demonstrate a significant VAT reduction by 15.2% after 26 weeks treatment with tesamorelin, while those individuals on placebo had a 5% increase in VAT [23]. HIV-infected individuals identified to be responders to tesamorelin based on VAT reduction of at least 8% demonstrated a more favorable metabolic profile over 52 weeks, such as improved triglycerides and adiponectin levels and maintenance of glucose homeostasis [24]. In addition to targeting VAT accumulation, a 6 month study demonstrated modest effects on liver fat reduction in those HIV-infected individuals randomized to tesamorelin vs. placebo independent of weight changes [25]. Liver fat reduction is mechanistically plausible, as treatment with a GHRH analog may have direct effects on liver fat through reducing hepatic de novo lipogenesis or indirect effects through oxidation of the visceral fat depot. Evidence also suggests there could be modest benefit on inflammation in HIV [26], which needs to be elucidated further and may be related to VAT reduction. Similar to GH treatment, withdrawal of GHRH may result in VAT reaccumulation [27].

Based upon these published data, tesamorelin is currently the only FDA approved medication for use in HIV-associated lipodystrophy, particularly for those with evidence of lipohypertrophy. The medication is a once daily subcutaneous injection usually prescribed by an endocrinologist. Use of tesamorelin requires careful safety monitoring of IGF-1 and HbA1c levels. While the medication is generally tolerated, rare side effects include injection site reactions, arthralgias, myalgias, and peripheral edema. Observational studies are currently ongoing to determine the long term benefits and safety profile of tesamorelin.

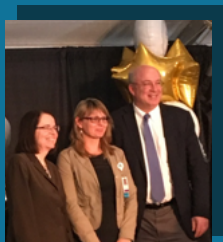
Further detailed studies are needed to understand the effects of GHRH analogues on other indices of cardiometabolic disease as well as cardiovascular mortality in HIV. Moreover, future investigations should determine whether similar cardiometabolic benefits may be achieved in other disease populations in which there may be relative GHD without evidence of pituitary disease and an increased risk of cardiometabolic disease, such as generalized obesity.

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### Agata Litra, Medical Assistant in the Massachusetts General Hospital Neuroendocrine and Pituitary Tumor Clinical Center, has been awarded a Partners in Excellence Award.

This award was bestowed on Ms. Litra because of her exceptional commitment to patient care. Ms. Litra is indispensable in the delivery of the highest quality care to our patients, who come from all over the country and world to our tertiary care pituitary center. She does everything she possibly can to help our patients directly and to aid physicians in taking care of Center patients, from greeting patients with warmth and compassion to tracking down lab results from laboratories outside MGH. Ms. Litra is key to the high quality care that the Center is able to provide, and we congratulate her on this extremely well-deserved award.



# Report from the Cushing's Disease Symposium at ENDO 2016

BEVERLY MK BILLER, MD

The 98th Annual Meeting of The Endocrine Society was held in Boston April 1-4, 2016. This article, adapted with permission from the Cushing's Support and Research Foundation Newsletter, summarizes talks given at a Symposium on the topic, "Cushing's Disease: An Update on Pathogenesis, Diagnosis, and Medical Treatment."

## Historical Note from Symposium Chair

In 2016, The Endocrine Society celebrated 100 years since the founding of the professional organization, with a theme called: "1916-2016, 100 years of hormone science to health". Selected Symposium Chairs were asked to provide a 5 minute Historical Note before introducing the three speakers for their sessions. For this Symposium on Cushing's disease (CD), held on April 2, 2016, I had the pleasure of delivering the Historical Note.

Dr. Harvey Cushing, known as the "father of modern neurosurgery" and the physician for whom CD is named, graduated from Harvard Medical School (HMS) in 1895. He served an internship (then termed "house pupil"), at Massachusetts General Hospital. Dr. Cushing was a surgical resident at Johns Hopkins Hospital and then returned to Boston as a faculty member at HMS. Dr. Cushing made many key discoveries about the pituitary gland, publishing *The Pituitary Body and its Disorders, Clinical States Produced by Disorders of the Hypophysis Cerebri* in 1912 (1).

Despite the fact that he was a neurosurgeon, Dr. Cushing served as the 3rd President of the Endocrine Society from 1920 to 1921. In his Presidential Address, Dr. Cushing equated the early stages of discovery in endocrinology to the voyage of a sailing ship, writing, "We find ourselves embarked on the fog-bound and poorly charted sea of endocrinology".

In 1932, Dr. Cushing identified the disorder that now bears his name by closely observing a number of patients with similar problems, describing this condition in the Bulletin of the Johns Hopkins Hospital (2). He correctly hypothesized that the condition was likely due to a small tumor in the pituitary gland.

He wrote, "I am quite aware that in ascribing the disorder to the basophilic elements (of the pituitary gland)...may arise questions which are at present unanswerable" (2). At that time, those questions included what caused these tumors to develop, what hormones were involved, how to measure them and how to treat the patients. He noted, "for states due to over-secretion, our only recourse at present is surgery or some form of radiation", predicting that, "the day is not too far distant when surgery will come to play a less...important role" (1). Nearly 90 years after Dr. Cushing made this statement, the first medications were approved by the FDA and EMA specifically to treat CD.

The speakers selected for this Symposium on **Cushing's Disease: An Update on Pathogenesis, Diagnosis, and Medical Treatment** were all involved in advances over recent years in the pathogenesis, diagnosis and treatment of the disorder, and have played a role in answering some of Dr. Cushing's questions from the early 1900s. They shared their knowledge about CD in this fascinating Symposium.

## Talk 1: New Concepts in Corticotroph Adenoma Pathogenesis and Experimental Treatments

By Dr. Gunter K. Stalla, Department of Internal Medicine, Endocrinology and Clinical Chemistry Max Planck Institute of Psychiatry, Munich, Germany

In past years, many genetic studies have been performed in Cushing's pituitary tumors in attempts to find mutations that explain how these tumors develop. This is important for identifying potential drug targets. However, mutations had been found only in very rare individual cases and in rare genetic syndromes.

## USP8 Mutations and Epidermal Growth Factor Receptor (EGFR)

More recently, mutations were found in the ubiquitin-regulating gene USP8. A large multicenter, retrospective study in Germany, UK, NIH/US, France, Brazil, Serbia and Hungary showed that somatic USP8 mutations were found in 40% of cases of CD and were more frequent in younger women (3).

USP8 is an enzyme which interacts with EGFR, which in turn, regulates cell growth. Mutated USP8 results in increased quantities of EGFR in corticotroph tumor cells. EGFR regulates p27 and Cyclin E; proteins that tightly control cell growth; they are present in different quantities in Cushing's pituitary tumors compared to normal pituitary tissue.

Data have shown that the EGFR present in Cushing's pituitary tumor cells also plays an important role in the regulation of ACTH production. Stimulation of EGFR increases ACTH secretion and inhibition reduces it. The evidence that EGFR controls cell growth and ACTH secretion makes it a potential target for medical treatment of CD.

## Hsp90 and Silibinin

Pituitary tumors causing CD continue to produce excess ACTH in the presence of excess cortisol as they are not responsive to normal feedback inhibition. This likely means that tumor cells are resistant to some control mechanism involving the glucocorticoid receptor (GR), the protein that interacts with cortisol. The mechanism whereby this occurs has not been fully understood.

A specific protein present in normal pituitary cells, called Hsp90, influences the 3D structure of GR and is necessary for tissue response to glucocorticoids. In tumors from CD patients, increased Hsp90 was noted in tumor cells compared to normal pituitary cells (4). Investigators hypothesized that increased levels of Hsp90 could lead to lower levels of the proper GR 3D structure required to respond to glucocorticoids; they investigated the effect of several Hsp90 inhibitors. In 5 out of 6 tumor cell cultures, silibinin (a natural substance used to treat mushroom poisoning in humans), increased the number of functional GR, restored responsiveness to glucocorticoids and decreased ACTH secretion. This was also confirmed in a mouse model (4). Studies in human patients with CD are expected.

## Talk 2: Laboratory Diagnosis of Cushing's Disease: Advances and Pitfalls By Hershel Raff, PhD, Aurora St Luke's Medical Center Medical College of Wisconsin, Milwaukee, WI

### 1) Screening Tests

The three major screening tests to use when the diagnosis of Cushing's syndrome is suspected are late-night salivary cortisol measurement

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Report from the Cushing's Disease Symposium at ENDO 2016 - Continued

(LNSC), an overnight low dose dexamethasone suppression test, and a 24 hour urine free cortisol (5). These three tests interrogate different aspects of the pathophysiology of Cushing's syndrome:

**Late-night salivary cortisol** – Normally, cortisol is highest in the morning and lowest at bedtime or soon thereafter. An increased LNSC level indicates a disrupted diurnal rhythm. In general, measurement of LNSC is considered the simplest and most accurate approach.

**Overnight dexamethasone test** – When cortisol is too high, production of cortisol is decreased to maintain normal levels through negative feedback on pituitary ACTH production. Dexamethasone is a potent synthetic steroid; thus, if blood cortisol remains increased when a low dose of dexamethasone is administered, it indicates decreased glucocorticoid negative feedback sensitivity, a typical feature of most tumors causing Cushing's syndrome.

**24 hour urine free cortisol** - Increased cortisol in the blood leads to increased filtration of free cortisol through the kidney and, hence into the urine. This test is not as sensitive as the other two measurements because it is often not increased until Cushing's syndrome is more severe.

**2) Differential Diagnosis**

Once Cushing's syndrome is established, it is critical to determine the cause. It can be due to a tumor in the adrenal gland making too much cortisol independently of ACTH or due to ACTH overproduction either from a pituitary ACTH-secreting adenoma (CD) or a non-pituitary source of ACTH (ectopic ACTH). Usually measuring a morning plasma ACTH is sufficient to distinguish an adrenal cause (suppressed ACTH) from a pituitary or ectopic cause (non-suppressed ACTH). If ACTH-dependent Cushing's syndrome is established, one must differentiate a pituitary from an ectopic tumor. If a pituitary lesion is clearly demonstrated by MRI (there is controversy over what size this should be), then a referral to a highly experienced pituitary neurosurgeon is warranted. If the MRI is negative (or shows only a small lesion), then inferior petrosal sinus sampling is performed in which catheters are threaded from groin veins up to the veins draining the pituitary. By demonstrating increased ACTH in the pituitary venous outflow, one can determine whether the cause is a pituitary ACTH-secreting tumor (CD).

Once CD is established, the typical first approach is transsphenoidal pituitary surgery. This must be done by an experienced neurosurgeon who has successfully operated on many patients with CD.

**3) Determination of Remission or Recurrence**

Unfortunately, surgical failures occur even in the best of neurosurgical hands and are usually detected in the post-operative period by a failure to have decreases in serum or urine cortisol or a persistently increased LNSC. However, even when patients are placed in remission, recurrences may happen many years later. The best way to monitor patients for recurrence is with occasional (perhaps every 6 - 12 months) measurements of LNSC. If the patient starts to experience recurrent symptoms, this test should be done immediately.

*Talk 3: Selecting a Target in Refractory Cushing's Disease: Corticotroph Tumor, Adrenal Steroidogenesis, or Glucocorticoid Receptor?*  
By Maria Fleseriu, MD, FACE, Departments of Medicine and Neurological Surgery, Northwest Pituitary Center, Oregon Health & Science University, Portland Oregon

Transsphenoidal surgery represents the first line of treatment for CD. However, even with an experienced neurosurgeon, some patients do not achieve remission and approximately 25% of patients eventually experience a recurrence. Medical treatment may then be needed. Medications can target 1) a pituitary tumor, 2) the adrenal glands to decrease cortisol synthesis, or 3) block the glucocorticoid receptor which decreases the effects of cortisol. A comprehensive discussion of available medical treatments is found in the Endocrine Society Clinical Guidelines on treatment (6). This talk focused on new drugs in development.

**PASIREOTIDE LAR**

Twice daily pasireotide is approved and targets the pituitary tumor. A once-monthly, intramuscular long-acting-release (LAR) formulation of

pasireotide approved for the treatment of acromegaly is now being evaluated for use in Cushing's disease (CD). In a phase III trial of 150 patients with persistent, recurrent or de novo (if not surgical candidates) CD, normalization of 24 hr urinary free cortisol (UFC) was observed in 40% of patients treated with pasireotide LAR for a duration of 7 months. Similar to twice daily pasireotide, high blood sugar was noted in 68% or 80% depending on the dose.

**OSILODROSTAT (LCI699)**

Osilodrostat is an oral inhibitor that blocks the final step in cortisol synthesis, similar to metyrapone. However, it is significantly more potent and has a longer half-life, allowing twice daily administration. In a 10-week, proof of concept study, osilodrostat normalized UFC in 11 of 12 patients with CD (7). An extension phase study enrolled an additional 15 new patients. At 22 weeks, response was seen in 78.9% and all responders had normal UFC levels (8). Common side effects were adrenal insufficiency, nasopharyngitis, nausea, diarrhea, and asthenia. Elevated testosterone levels and hirsutism or acne were noted in 3 of 11 females. Based on these results, osilodrostat shows promise and two phase III studies (clinicaltrials.gov; NCT02180217 and NCT02697734) are currently underway.

**Research Studies Available**

Patients may qualify for research studies in the Neuroendocrine Unit. 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
Adults with Growth Hormone Deficiency	• Long acting GH replacement study	BMK Biller, MD Karen Liebert, RN
Adults with Cushing's	• Treatment study assessing the effect of an investigational medication on cortisol levels	BMK Biller, MD Karen Liebert, RN
Adults with active or treated acromegaly	• Quality of life • Cross-sectional bone density study • Study evaluating sustained control with oral octreotide	Pouneh Fazeli, MD Lisa Nachtigall, MD Karen Liebert, RN
Men with hypopituitarism	• Characterization of oxytocin deficiency	Elizabeth Lawson, MD

*The Neuroendocrine Unit 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 (pituitary.mgh.harvard.edu) for more information about potential studies which may not be listed here.*

#### LEVOKETOCONAZOLE (COR-003)

Levoketoconazole is an investigational new drug for CS that acts similarly to, but is hypothesized to provide better safety and efficacy than closely related ketoconazole. Higher potency theoretically may allow lower doses and fewer adverse events. Levoketoconazole is 12 times less potent at inhibiting a key liver enzyme, thus less hepatic toxicity might be expected with this medication. A phase III single-arm, open-label trial is currently ongoing to evaluate the efficacy, safety, tolerability, and pharmacokinetics of levoketoconazole in patients with Cushing's (clinicaltrials.gov; NCT01838551).

#### R-ROSCOVITINE

R-roscovitine, an inhibitor of Cyclin E (discussed by Dr. Stalla), has been evaluated as a potential therapy for CD patients. R-roscovitine was first shown to be effective in reducing ACTH and corticosterone serum levels in a mouse model (9). Currently, a phase II clinical trial (clinicaltrials.gov; NCT02160730) in human patients with CD is underway to evaluate the efficacy and safety of R-roscovitine.

#### RETINOIC ACID

Retinoic acid was proposed as a treatment for CD patients after it was shown to decrease ACTH secretion and pituitary tumor growth in cell culture and in animal models. A clinical trial demonstrated that a specific form of retinoic acid, isotretinoin, resulted in UFC normalization in 4 of 16 patients (25%) at 12 months, with UFC reductions up to 52% seen in the rest. Mild and reversible adverse events, were reported in over 40% of patients (10). Further randomized, double-blind, clinical trials are needed in patients with CD.

#### EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS

As discussed by Dr. Stalla, mutations in corticotroph tumors involve the USP8 gene, which interacts with EGFR. Gefitinib, an EGFR inhibitor currently approved for treatment of some cancers, reduced ACTH secretion and tumor size, resulting in clinical improvement in animal models. Thus, inhibition of EGFR has potential therapeutic application in CD and a study is underway (clinicaltrials.gov; NCT02484755).

#### CONCLUSION

The symposium on Cushing's Disease at ENDO 2016 highlighted recent advances in the pathophysiology, diagnosis and treatment of this challenging condition. As Karen Campbell, a leader of the patient support organization Cushing's Support and Research Foundation, noted after attending the Symposium, "While great progress has been made in the last 100 years, there is still much work to do.....who knows what the area of Cushing's will look like in another 100 years!"

Dr. Biller has a consulting relationship with the following companies: Cortendo, Ipsen, and Novartis.

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## The Neuroendocrine and Pituitary Tumor Clinical Center Welcomes Drs. Laura Dichtel and Melanie Schorr



Dr. Laura Dichtel earned her medical degree at the Yale University School of Medicine and then completed her residency training at Brigham and Women's Hospital and fellowship in endocrinology at the Massachusetts General Hospital (MGH). At MGH, Dr. Dichtel sees patients with pituitary and neuroendocrine disorders. In addition, Dr. Dichtel is an attending physician on the inpatient consult service, teaches medical students and residents, and performs clinical research in the Neuroendocrine Unit.



Dr. Melanie Schorr completed her medical degree at the Johns Hopkins University School of Medicine, and was an internal medicine resident at the Brigham and Women's Hospital. Her endocrinology fellowship was conducted at the Massachusetts General Hospital (MGH). Dr. Schorr sees patients with pituitary and neuroendocrine disorders at the Neuroendocrine and Pituitary Tumor Center at MGH. In addition, she is involved with inpatient consultations, teaching and conducting clinical research studies.

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### 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. doctrine and Pituitary Tumor Clinical Confer

A weekly interdisciplinary conference is held to discuss all new patients referred to the 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](mailto:pituitary.info@partners.org).

### SCHEDULING

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

### ACKNOWLEDGEMENTS

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