Hypophysitis Associated With Immune Checkpoint Inhibitors

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Background

Immune checkpoint inhibitors (CPIs) have transformed the landscape of oncology since the approval of ipilimumab by the US Food and Drug Administration in 2011. Eighteen cancer types are currently approved for treatment with 7 CPIs (ipilimumab, nivolumab, pembrolizumab, cemiplimab, atezolizumab, durvalumab, and avelumab). A recent study estimated that almost half of all patients with cancer in the United States are eligible for treatment with CPIs, a proportion far outweighing those eligible for genome-targeted therapies (1-2).

Ipilimumab is an IgG1-based monoclonal antibody. Canonically, its effects are mediated through the inhibition of cytotoxic T-lymphocyte antigen-4 (CTLA-4) on activated T cells. CTLA-4 competitively binds B7 to block costimulation and thereby downregulates T cell activation and proliferation, acting as a brake on the immune response. Nivolumab, pembrolizumab, and cemiplimab are IgG4-based monoclonal antibodies targeting programmed cell death 1 (PD-1). Atezolizumab, durvalumab, and avelumab are IgG1-based monoclonal antibodies that inhibit programmed death-ligand 1 (PD-L1). PD-1 is expressed by activated T and B lymphocytes and monocytes; PD-L1 is found on antigen-presenting cells and many other cell types. Binding of PD-1 to PD-L1 inhibits the immune response of these cells primarily at the level of the tumor microenvironment (3-4). Tumoral expression of PD-L1 and/or PD-L2 can act as a mechanism of evasion from immune surveillance.

Immune-related adverse events (irAE) occur in some patients as sequelae from CPI treatment and can involve any organ system. Potential endocrine irAEs include hypophysitis, primary hypothyroidism with or without destructive thyroiditis and temporary thyrotoxicosis, hyperthyroidism due to Graves disease, diabetes mellitus, primary adrenal insufficiency (AI), and hypoparathyroidism. Primary hypophysitis is a rare disorder with an estimated annual incidence of 1 in 7-9 million (5), and it accounts for less than one percent of pituitary surgery cases (6-10). Hypophysitis secondary to CPIs is a recently recognized clinical entity and has likely become the most frequent etiology for new hypophysitis cases.

Epidemiology

The risk of hypophysitis after treatment with ipilimumab is significant. Pooling the largest endocrinology-focused studies yields an overall risk of approximately 10% following treatment with ipilimumab monotherapy (145/1,394-1,438) (11-18). The frequency of hypophysitis following anti-PD-1 treatment is much lower and appears to be less than 1% (17/3,522) (13). Whether combination therapy with ipilimumab plus anti-PD-1 agents increases the risk of hypophysitis has not yet been fully determined. No endocrinology study has addressed this question yet. Data derived from prospective oncology studies may be significantly limited by multiple inadequacies of the endocrinology categories in the Common Terminology Criteria for Adverse Events, many of which are imprecise and overlapping. Hypophysitis appears to be rare following treatment with agents targeting PD-L1, but available data are limited. No endocrinology study or review of oncology studies has analyzed this population. Male gender appeared to be a risk factor for ipilimumab-associated hypophysitis in one study (14) but not others (12, 15-17). It is unclear if age is a risk factor for hypophysitis after treatment with ipilimumab. The influence of age and gender has not been examined for anti-PD-1 and PD-L1-associated hypophysitis.

Presentation and Diagnosis

The clinical presentation of hypophysitis appears to be distinct in patients receiving ipilimumab compared to

Figure 1. Time (weeks) from the onset of therapy until the diagnosis of hypophysitis for patients treated with anti-PD-1 monotherapy (Panel A), ipilimumab monotherapy (Panel B) and ipilimumab plus concurrent nivolumab (Panel C). Reproduced with permission from Faje et al., European Journal of Endocrinology, 2019 (13).
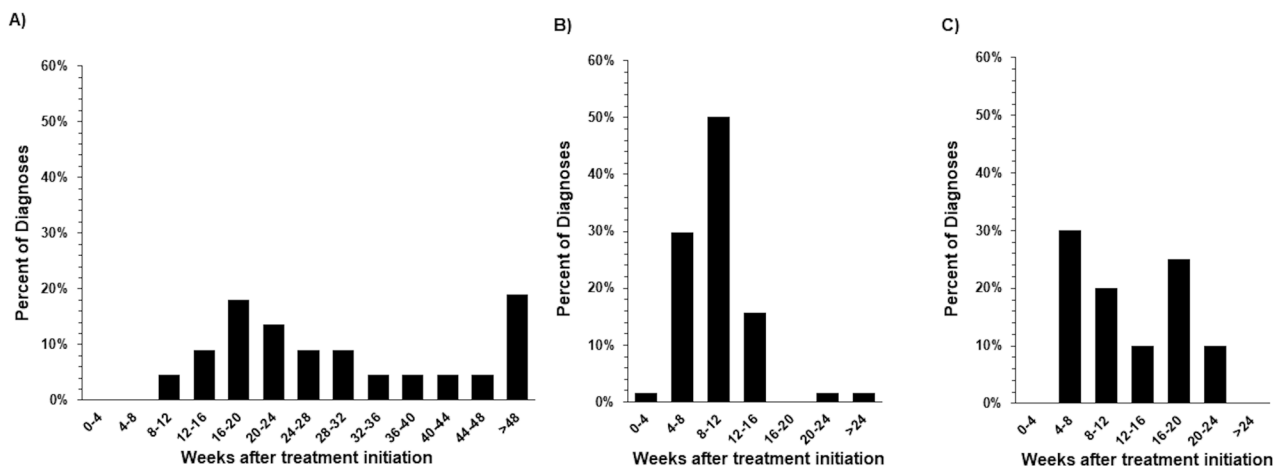
those receiving anti-PD-1 therapy. Hypophysitis develops relatively soon after treatment initiation with ipilimumab, typically after 2 or 3 cycles of therapy. Hypophysitis may be diagnosed over a much broader period of time in patients treated with anti-PD-1 agents, in some cases nearly a year after starting therapy (Figure 1). Headache is a frequent presenting symptom in ipilimumab-associated hypophysitis but uncommonly occurs in anti-PD-1 hypophysitis patients. Concordant with that difference, radiographic pituitary enlargement occurs in nearly all ipilimumab hypophysitis patients but is observed in only a minority of anti-PD-1 hypophysitis cases. Hyponatremia is common in both groups and may be a sign of hypothyroidism and/or AI. Generalized fatigue, loss of appetite, and myalgias/arthralgias are the primary symptoms in anti-PD-1 hypophysitis patients. Isolated central AI is typical in hypophysitis associated with anti-PD-1 agents; multiple anterior pituitary hormone

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deficiencies occur more commonly in hypophysitis associated with ipilimumab. Diabetes insipidus is extremely rare in both groups. Combination therapy (ipilimumab plus anti-PD-1 treatment) hypophysitis patients share characteristics of both monotherapy groups but appear to align much more closely with ipilimumab-associated hypophysitis (13,19).

No case of CPI-associated hypophysitis has been confirmed by surgical biopsy. An autopsy specimen has been described

from a single case of tremelimumab-associated hypophysitis (tremelimumab is an IgG2-based anti-CTLA-4 antibody) (20). Clinical diagnoses of CPI-associated hypophysitis are based on the presence of new hypopituitarism and/or new reversible radiographic pituitary enlargement following treatment with CPIs in the absence of an alternative etiology. A serial decline in TSH values may precede the onset of ipilimumab-associated hypophysitis (19,21), and radiographic changes may also occur before the onset of clinical symptoms in these patients (14). Pituitary gland enlargement is generally mild, rarely compresses the optic apparatus, and may only be appreciated in some cases after comparison with prior imaging (19). Gland enlargement exists for only a brief time in some patients and may be missed if imaging is delayed (Figure 2) (22). Pituitary function test results may be influenced by factors such as recent or current exogenous glucocorticoid use, chronic illness and associated factors such as nutritional status, and/or the presence of an additional endocrine irAE in some patients. Due to the nonspecific character of their presenting symptoms, the frequent lack of localizing features, and typically negative imaging findings, diagnosis may be particularly challenging in anti-PD-1 hypophysitis cases; awareness is key.

Treatment and Outcomes

The precise therapeutic role of pharmacologic dosages of glucocorticoids in primary hypophysitis remains somewhat ill-defined. Early treatment strategies by many groups for ipilimumab-associated hypophysitis also incorporated supraphysiologic dosages of glucocorticoids. Multiple studies have reported that high dosages of glucocorticoids utilized for the treatment of irAEs do not appear to inhibit the antitumor efficacy of CPIs (23-30). Notably, some studies suggest that the development of an irAE may be associated with higher tumor response rates (24-25,28-30). Ipilimumab-associated hypophysitis likewise may be correlated with improved survival in patients with melanoma (22). The

presence of an irAE may therefore represent a confounding factor in analyses assessing the impact of pharmacologic glucocorticoids on CPI antitumor efficacy. Ipilimumab-associated hypophysitis patients treated with physiologic or near-physiologic dosages of glucocorticoids appear to have improved overall survival, progression free survival, and time to treatment failure compared to those receiving high dosages. Additionally, higher dosages of glucocorticoids do not hasten the resolution of pituitary gland enlargement or help recover pituitary function in these patients (22). Limited additional studies have suggested similar potential negative antitumor effects from pharmacologic dosages of glucocorticoids in patients treated with CPIs (31-33). Given the apparent lack of benefit and questionable negative effects from higher dosages, physiologic glucocorticoid replacement appears to be appropriate for most patients with ipilimumab-associated hypophysitis and is also a reasonable management strategy for cases of hypophysitis associated with anti-PD-1 or PD-L1 therapy.

Central AI appears to be permanent in nearly all patients with CPI-associated hypophysitis. Other hormonal axes may recover in some patients (13,19,22). Treatment of central hypothyroidism with thyroid hormone replacement is appropriate at the time of diagnosis. Thyroid hormone weaning/withdrawal may be attempted at a future date in suitable patients. Gonadal hormone replacement can be deferred initially if appropriate in order to assess for potential axis recovery. Growth hormone replacement is contraindicated in patients with CPI-associated hypophysitis due to the underlying malignancy.

Mechanism of CPI-associated Hypophysitis and Potential Therapeutic Application

Ipilimumab-associated hypophysitis may occur secondary to direct drug binding and targeting of the pituitary gland. CTLA-4 is expressed by anterior pituitary cells in mice and humans. CTLA-4 expression levels in humans appear to be highly variable (20,34-35). Experiments *in vitro* with a melanoma cell line and *ex vivo* with T regulatory cells have demonstrated that ipilimumab can activate antibody-dependent cellular cytotoxicity (36-37). Mice injected with anti-CTLA-4 antibody show activation of the classical complement pathway and complement deposition onto anterior pituitary cells. In the previously noted autopsy case of tremelimumab-associated hypophysitis, the patient had a high expression level of CTLA-4 in the anterior pituitary, evidence of IgG2 binding, complement deposition, abundant macrophage infiltration as well as T and B cells consistent with type II and IV hypersensitivity reactions, and a lack of posterior pituitary gland involvement (consistent with the lack of diabetes insipidus observed in CPI-associated hypophysitis patients) (20,34). Coherent with the hypothesis that drug binding to anterior pituitary cells is important for the development of ipilimumab-associated hypophysitis, 2 studies of 25 patients with germline CTLA-4 mutations reported the presence of multiple severe autoimmune diseases but no case of hypophysitis/hypopituitarism (38-39).

It is unknown whether PD-1 is expressed by pituitary cells. Regardless, anti-PD-1 medications are IgG4-based antibodies, which have a poor ability to bind complement and activate Fc receptor subtypes (40-41). The anti-PD-L1 medications atezolizumab and durvalumab cannot effectively bind Fc receptors or complement due to modified Fc domains.

Figure 2. Images from a patient with ipilimumab-associated hypophysitis. Radiographic pituitary gland enlargement developed over a 4-day period and resolved equally quickly followed by a gradual evolution to a nearly empty sella. Panels A) Prior to treatment with ipilimumab, B) 4 days prior to the diagnosis of hypophysitis, C) hypophysitis showing gland enlargement, D) 4 days after diagnosis, E) 19 weeks post-diagnosis. Adapted from Faje et al., Cancer 2018 (22).
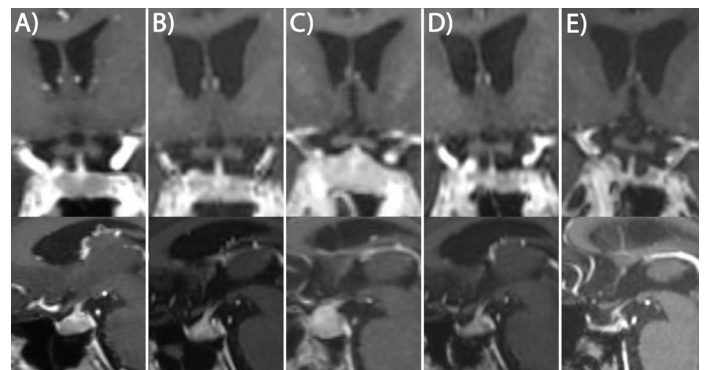
The possibility that ipilimumab may directly target pituitary tissue suggests that the off-target effect of hypophysitis could potentially be harnessed for therapeutic treatment of selected aggressive pituitary tumors and carcinomas (19). In a recent case report, combination therapy with ipilimumab plus nivolumab was successfully utilized in the treatment of an ACTH-secreting pituitary carcinoma (42). Tumor mutational burden is correlated with response rates for ipilimumab and anti-PD-1 therapy within individual cancer types and across different malignancies (43-46). The authors of the case report hypothesized that a higher tumor mutation load following prior treatment with temozolomide was a significant factor for the tumor's response to CPI treatment (42). Whether mutational burden or alternatively CTLA-4 expression is related to CPI treatment response in these tumors deserves further investigation.

Key Points

- Checkpoint inhibitors (CPIs) occupy an expanding role in the treatment of a broad range of malignancies, and consequently CPI-associated hypophysitis has become a more frequently encountered irAE.

- Hypophysitis is a more common side effect following treatment with ipilimumab compared to other CPIs.

- The time of onset and clinical presentation of

hypophysitis differs between ipilimumab and other CPIs. Hypophysitis develops relatively soon after ipilimumab treatment initiation, and radiographic pituitary gland enlargement, headache, and multiple anterior pituitary hormone deficiencies are observed more commonly in ipilimumab-associated hypophysitis. These clinical differences may result from distinct underlying mechanisms of toxicity.

• Supraphysiologic dosages of glucocorticoids do not appear to be advantageous in the treatment of CPI-associated hypophysitis.

• CPIs may have an application in the treatment of selected aggressive pituitary adenomas and carcinomas.

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Impulse Control Disorders with Dopamine Agonists

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Historical Case Presentation

A 20 year old male underwent head imaging to evaluate headaches. Incidentally, he was found to have a macroprolactinoma and underwent a transsphenoidal resection for initial treatment. After this transsphenoidal resection, bromocriptine became available for use and he was subsequently initiated on dopamine agonist therapy for his hyperprolactinemia and residual tumor. He did not have a history of psychiatric disease prior to initiation of medical therapy. He eventually was transitioned from bromocriptine to cabergoline after transferring his endocrine care to a different provider. After several years on cabergoline, he began to notice increased gambling and hypersexuality as well as depressed mood. These behaviors began to affect his marriage, at which time he discussed them with his endocrinologist. His cabergoline dose was subsequently reduced; and after this reduction, the gambling and hypersexuality behaviors resolved and his mood improved. Despite resolution of these behaviors, these symptoms contributed the eventual dissolution of his marriage.

Case Commentary

This patient presented in the 1970s, just prior to the availability of bromocriptine for hyperprolactinemia; thus surgery was the initial treatment. Note that if we were managing the patient at the time he first experienced an impulse control disorder, the dopamine agonist would have been discontinued, as this provides the highest likelihood of symptom resolution.

What are impulse control disorders?

Impulse control disorders (ICDs) include a class of psychiatric conditions characterized by impulsivity such as pathological gambling, hypersexuality, compulsive shopping and/or eating, and punding (repetitive mechanical tasks such as assembling objects). (1-2) ICDs have been reported with the use of dopamine agonists (DAs) in a variety of clinical settings including in the treatment of Parkinson's disease (3-4) and restless leg syndrome. (5) More recently, ICDs are described among patients being treated with DAs for prolactinomas and hyperprolactinemia, conditions where the doses of DAs tend to be lower than those used in the treatment of Parkinson's disease.(6) The presence of these behaviors in the setting of DA therapy is thought to be related to stimulation of the mesolimbic dopamine receptors in the central dopaminergic reward system. (4) As with the patient in the case above, ICDs can have a significant economic, health, and social impact on patient lives.

What have studies on impulse control disorders in the setting of DA for treatment of prolactinomas and/or hyperprolactinemia demonstrated?

In Martinkova et al., investigators reviewed the cases of 20 patients who were consecutively seen in 2009 by an endocrinologist for treatment of a pituitary adenoma using a DA and underwent a Minnesota Impulse Disorder Interview (MIDI) focusing on ICDs. (7) Patients were classified as having ICDs according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Two of the 20 patients being treated with a DA were classified as having an ICD. One of these patients developed compulsive eating on bromocriptine, leading to a 20kg weight gain and later developed compulsive gambling after being switched to cabergoline. He eventually underwent partial resection of his pituitary adenoma and radiation therapy and was maintained on a lower dose of cabergoline. The second patient developed hypersexuality while on bromocriptine 15mg daily; with evidence of a decrease in the size of his pituitary adenoma, his bromocriptine dose was reduced, resulting in a reduction in his hypersexuality. In both of these cases, the ICD negatively impacted their personal lives. Moreover, in one of the patients, the behaviors continued even after switching to a different dopamine agonist. The patients also appeared to exhibit the behaviors in a dose dependent manner, such that at lower doses they exhibited these behaviors less.

In a cross-sectional study, Bancos et al., compared the frequency of ICDs among patients with prolactinomas and past or current use of a DA versus patients with non-functioning pituitary adenomas (NFPAs) and no history of DA use. (8) Participants underwent a hypersexuality questionnaire, MIDI, modified South Oaks Gambling Screen, and punding questionnaire. In this study, males with prolactinomas on DA were found to be close to ten times more likely to develop an ICD compared to males with NFPAs who were not on a DA. In different study performed by Barake et al. at the Neuroendocrine and Pituitary Tumor Clinical Center at Massachusetts General Hospital, investigators compared indices of impulsivity between 3 different groups – hyperprolactinemia patients on DA therapy, hyperprolactinemia patients not on DAs, and normoprolactinemic patients with presumed Rathke's cleft cyst or NFPA. (9) Patients underwent a Behavioral Inhibition/ Activation System (BIS/BAS) questionnaire and the Barratt Impulsiveness Scale (BIS-11). Higher scores on the attention subscale of the BIS-11 were found among the hyperprolactinemic patients on a DA compared to the hyperprolactinemic patients not on a DA and the normoprolactinemic group. Moreover, there was a direct relationship between increased impulsivity and weekly cabergoline dose.

In a prospective, longitudinal study performed at Cerrahpasa Medical School in Istanbul, Turkey by Celik et al., participants underwent screening for the presence of ICDs by completion of a revised MIDI, Symptom Checklist (SCL-90-R) questionnaire, BIS, Beck Depression Inventory (BIDI), and Beck Anxiety Inventory (BAI). (10) Participants who were

Table 1. Summary of studies describing ICDs and/or impulsivity among patients receiving dopamine agonist therapy for prolactinomas and/or hyperprolactinemia

Study	Type of Study	Patient population	Dose-response relationship with DA present	Any ICD prevalence
Martinkova, et al. 2011 (7)	Case Review	Single Group: - Pituitary adenoma on DA	Yes	10% (2/10)
Bancos, et al. 2014 (8)	Cross-sectional	Two groups: - Prolactinoma on DA - NFPA not on DA	No	Whole group: 25% (19/77) vs. 17% (12/70) (ns) Male only: 28% (13/47) vs. 4% (1/27) (P=0.01)
Barake, et al. 2014 (9)	Cross-sectional	Three groups: - Hyperprolactinemia on DA - Hyperprolactinemia not on DA - Rathke's cleft cyst and NFPA not on DA	Yes	- ICD prevalence not reported - Higher attentional score on BIS-11 questionnaire
Celik, et al. 2018 (10)	Longitudinal	Three groups - Prolactinomas on DA - Non-functioning adenomas not on DA - Healthy controls without known pituitary adenoma not on DA	Yes	8% (2/25) in prolactinoma group
Dogansen, et al. 2019 (11)	Cross-sectional	Single group: - Prolactinoma on DA	No	17% (51/308)
De Sousa, et al. 2019 (12)	Cross-sectional	Two groups: - Hyperprolactinemia on DA - Healthy controls without known pituitary adenoma not on DA	No	61% (69/113) vs. 42% (42/99) (P=0.01)

Abbreviations: BIS-11, Barratt Impulsiveness Scale-11; DA, dopamine agonist; ICD, impulse control disorder; NFPA, non-functioning pituitary adenoma; ns, non-significant

suspected of having an ICD based on these questionnaires underwent further evaluation by psychiatrists. This evaluation was repeated for participants on DAs at the 3rd and 12th month of drug therapy. In addition to a cohort of participants with prolactinomas that were on DAs, this study also included a cohort of participants with NFPAs not on a DA and healthy controls not on a DA. Participants with past or current ICDs or major psychiatric or mental disorders were excluded. Two patients on DA (8% of those in the prolactinoma group) developed an ICD associated with hypersexuality which stopped or was reduced with discontinuation of the DA. Additionally, the cumulative DA dose was directly related to several components of the SCL-90-R, including obsession, interpersonal sensitivity, paranoid ideation, hostility, and phobic anxiety subscales but not with the development of an ICD. The exclusion of participants with a history of past or current ICDs or major psychiatric disorder in this study may have affected the incidence of ICDs found in this particular study.

More recently, in a cross-sectional multicenter study, Dogansen et al. found that 17% of patients with prolactinomas on DAs for at least 3 month had at least one ICD. (11) In this particular study, the presence of an ICD was ascertained using section 1 of the Questionnaire for Impulse-Compulsive Disorders in Parkinson's disease (QUIP) and the BIS-11. The prevalence of any ICD varied with respect to follow-up period (35% in patients with follow-up period ≤ 12 months vs. 11% in patients with a follow-up period > 12 months), whereas the type of ICD varied by sex with hypersexuality being more common among male patients and compulsive shopping being more prevalent among female patients. While this study did not include a group of control participants, a more recent study by De Sousa et al. investigated ICD prevalence among hyperprolactinemic patients on DA versus healthy controls. (12) The presence of an ICD was determined by several questionnaires, including the Depression Anxiety Stress Scale (DASS21), a shortened version of the QUIP (QUIP-S), Hypersexual Behavior Inventory (HBI), Hypersexual Behavior Consequences Scale (HBCS), and Social Desirability Response Set Scale (SDR55). Patients treated with DA were more likely to have any ICD (based on the QUIP-S) compared to controls (61.1 vs 42.4%). In particular, there was an increased prevalence

of hypersexuality, compulsive buying, and punding among patients treated with DA compared to controls. This study had a higher prevalence of ICD as compared to prior studies. One possible reason for this is that unlike prior studies such as Celik et al., this study did not exclude participants with a history of ICD or other major psychiatric disorder. Moreover, investigators also found several independent predictors of an ICD, including male sex, eugonadism, and psychiatric comorbidity; DA dose, however, was not found to be predictive of ICD. Notably, higher testosterone levels at baseline conferred a trend toward a higher risk of hypersexuality, suggesting that the development of hypersexuality in men receiving DA is not related solely to improvements in testosterone levels with treatment of their hyperprolactinemia.

Implications for patients on dopamine agonists

These studies imply that DAs may contribute to the development of ICD among patients receiving this class of medications for prolactinomas and hyperprolactinemia. While doses of DA used to treat these conditions are lower than those used to treat diseases such as Parkinson's, patients on DAs for these neuroendocrine indications may still exhibit ICDs even without known prior psychiatric disease. Because ICDs can be extremely serious, and there are other treatment options for prolactin disorders, we strongly advise discontinuation of DAs if ICDs develop. While discontinuation of DA therapy typically leads to cessation or a decrease in the behaviors seen with an ICD, the development of an ICD in these patients can still have significant life-long effects on a patient's personal life as exemplified by the patient case above. Currently, there are no standardized guidelines for screening for ICDs in patients who are on or will be initiated on DA therapy for prolactinomas and/or hyperprolactinemia. Further studies will be needed for the development of these standardized guidelines. While these studies are being developed, increasing the awareness of the potential for ICDs with DA therapy will be important for both the physicians who educate and counsel their patients about impulsivity with dopamine agonists and the patients who are currently on or will be initiated on such therapy.

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Research Studies Available

Patients may qualify for research studies in the Neuroendocrine and Pituitary Tumor 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
Adults with active or treated acromegaly	Study with a once a month, add-on therapy for those uncontrolled on highest dose of somatostatin analogues	Beverly MK Biller, MD Karen Pulaski Liebert, RN
	Studies for those on a somatostatin analogue or on combination therapy investigating a once daily, oral medication	

The Neuroendocrine and Pituitary Tumor Clinical Center is involved in many different research studies. Types of studies and enrollment status changes frequently, so please call our office (617-726-3870) or check our webpage (pituitary.mgh.harvard.edu) for more information about potential studies which may not be listed here.

Neuroendocrine & Pituitary Tumor Clinical Center (NEPTCC) Bulletin

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The Neuroendocrine and Pituitary Tumor Clinical Center is located on the 1st floor (Suite 140) of the Cox Building 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.

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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.

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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. This Service is supported in part by unrestricted educational grants from Chiasma, Strongbridge and Ipsen.

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

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