MASSACHUSETTS GENERAL HOSPITAL

Neuroendocrine & Pituitary Tumor Clinical Center (NEPTCC) Bulletin

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Macimorelin as a Diagnostic Test for Adult GH Deficiency

LAURA DICHTEL, MD

The evaluation for growth hormone deficiency (GHD) is an important step in the management of adults with known or suspected pituitary disorders. Growth hormone (GH) replacement has been shown to have positive effects on body composition, muscle mass, bone density, liver health and quality of life (1). However, GH replacement is an expensive therapy and carries the burden of daily injections for patients. Thus, accurate diagnostic testing is critical to identifying patients with true GHD who may benefit from GH replacement.

The insulin tolerance test (ITT) is considered the gold standard test for the diagnosis of adult GHD. However, this test requires induction of hypoglycemia and is thus contraindicated in the elderly, those with seizure disorders or cardiovascular disease. Growth hormone releasing hormone (GHRH)-arginine testing was previously available in the United States for testing of GHD, which offered an alternative testing procedure with established cut-offs stratified by body mass index (2). However, GHRH was withdrawn from the U.S. market in 2008, although it is still available in other markets. Glucagon stimulation testing has remained as a viable alternative to the ITT in the U.S., however, it requires an IM injection, 3-4 hours of testing time and can cause nausea and vomiting (1,3-5).

Macimorelin, a ghrelin analog, is a GH secretagogue that can be administered as an oral solution. Piccoli et al. established that oral administration of macimorelin led to rapid absorption and a substantial peak in GH levels in 36 healthy male volunteers between 50-75 minutes later with no adverse events (6). A subsequent study by Garcia et al. established that a GH cutoff of 2.7 ng/mL on oral macimorelin testing had 82% sensitivity and 92% specificity for the diagnosis of GHD in a population of 50 individuals with adult onset GHD versus controls matched for age, BMI, sex and estrogen status. This study was initially designed to compare the efficacy of macimorelin versus GHRH-arginine, however, the full protocol could not be completed once GHRH was withdrawal from the U.S. market (7).

More recently, Garcia et al. performed a randomized, open-label, two-way crossover trial to compare macimorelin with the standard ITT for diagnosis of adult GHD (8). They studied 139 adults age 18-65 years, including adults at risk for GHD as well as controls. The individuals at risk for GHD were subdivided into three categories based on their pituitary disease and other hormone deficits, including (A) high likelihood (n=38), (B) moderate likelihood (n=37) and (C) low likelihood of GHD (n=39). A fourth group (D) of controls (n=25) with no pituitary disorders were studied and matched to group A (high likelihood of GHD) for sex, age, BMI and estrogen status. Notable exclusions for all groups included age >65 years old, uncontrolled diabetes mellitus (hemoglobin A1C >8.0%) and extreme obesity (BMI >40 kg/m^2).

These individuals were randomized with regards to the order of the ITT and macimorelin testing. The ITT was performed per standard protocol with serum sampling for GH and glucose at 15, 30, 45, 60, 90 and 120 minutes after the administration of insulin. Macimorelin testing involved a dose of 0.5 mg/kg administered as an oral solution within a 30-minute window with serum sampling for GH at 30, 45, 60 and 90 minutes after administration.

In the current study, authors first compared the agreement between the results of macimorelin testing and the ITT. The predefined cutoffs were 5.1 ng/mL for the ITT and 2.8 ng/mL for the macimorelin test based on prior literature (5,7). Thus, the macimorelin test with a cutoff of 2.8 ng/mL and ITT with a cutoff of 5.1 ng/mL had a 95% negative agreement and 74% positive agreement, which translated to a low risk

of macimorelin overdiagnosing GHD but the possibility of underdiagnosis of GHD when compared to the gold standard ITT. A post-hoc analysis was completed using 5.1 ng/mL for both the macimorelin test and ITT, which demonstrated a similar negative agreement of 94% and improved positive agreement of 82%. Thus, using the higher cutoff for the macimorelin test led to fewer missed cases of GHD (fewer instances of underdiagnosis) with a similarly low rate of overdiagnosis when using the ITT as a gold standard.

In receiver operator curve analysis of subjects with presumed GHD (Group A / true GHD) and controls with no pituitary disorders (Group D / true controls), the *a priori* cutoff of 2.8 ng/mL was determined to have a sensitivity of 87% and specificity of 96% for the diagnosis of GHD, indicating that some cases of GHD would likely be missed using this cutoff. When the cutoff was increased to 5.1 ng/mL (identical to the traditional ITT cutoff), the sensitivity of the macimorelin test improved to 92% with unchanged specificity of 96%.

This study demonstrated that macimorelin testing was practical, with only one (0.6%, total n=154) non-evaluable test versus 27 (17%, total n=157) non-evaluable ITTs, mainly due to lack of achieved hypoglycemia for the latter test. Additionally, the reproducibility of the macimorelin testing was demonstrated to be 94% in a substudy of 33 patients. No serious adverse events were reported with either the ITT or macimorelin. Non-serious adverse events occurred much more frequently in the ITT versus macimorelin (761 events in 157 patients versus 77 events in 154 patients, respectively). The mild-to-moderate side effects reported with macimorelin included dysgeusia (4.5%), fatigue (3.2%), headache (2.6%) and nausea (2.6%). These were compared to those side effects most common with the ITT, including somnolence and hyperhidrosis (3.2% each), asthenia (2.5%), hunger (1.9%), nervousness (1.3%) and tremor (0.6%). Additionally, QTc prolongation on EKG was less frequent and generally milder in the macimorelin tests versus ITT. However, there do not appear to be good data regarding the use of macimorelin in patients already on QTc prolonging medications, and the authors of this study indicate that this could be an area of future investigation.

> *"macimorelin is a new option for GH stimulation testing that is orally administered, 90 minutes in length, reproducible, well tolerated and has published cutoffs with high sensitivity and specificity"*

Finally, in the 2013 study, Garcia et al. demonstrated that peak GH levels after macimorelin were inversely associated with BMI in controls (R=-0.37, P=0.01) (7). Multiple studies from our group and others have demonstrated that peak-stimulated GH with glucagon stimulation is lower in overweight and obese individuals compared to normal-weight controls (3,9). Given that the vast majority of subjects in this study (70%) had a BMI of <30 kg/m^2, this particular study is does not allow detailed evaluation of BMI-stratified peak-stimulated GH cutoffs.

In summary, macimorelin is a new option for GH stimulation testing that is orally administered, 90 minutes in length, reproducible, well tolerated and has published cutoffs with high sensitivity and specificity based on a population of adult patients with a BMI <30 kg/m^2. Further study will be needed to determine the effectiveness of this test in children, adults >65 years old and patients with hemoglobin A1C >8.0%.

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The Massachusetts General Hospital Neuroendocrine and Pituitary Tumor Clinical Center won a **Patient Experience Award** based on the actual ratings given by patients and their families. It is a recognition of all the hard work of the team throughout the year to make the patient experience responsive and compassionate. The photo depicts William McLaughlin III, Rodney Lomax, Jessica Spallone and Agata Litra, receiving the trophy at a Hospital ceremony.

CASE RECORDS OF THE MGH NEUROENDOCRINE AND PITUITARY TUMOR CLINICAL CENTER: When Do Prolactinomas Require Surgery?

Pamela S. Jones, MD, MS, MPH

A 22-year-old man presented to MGH Neurosurgical and Neuroendocrine and Pituitary Tumor Clinical Center with headaches and visual loss. He was referred by his ophthalmologist, who documented a temporal field defect with a dense right central scotoma. He had first noted near blindness in his right eye 2 months prior to presentation at his annual physical when he decided to test himself on the eye chart. He was then seen by an ophthalmologist who found right optic neuropathy and visual field testing consistent with severe right junctional scotoma and right afferent pupillary defect (Figure 1).

Besides decreased vision, he reported headaches attributed to migraines for the prior 6 months. He endorsed limited libido, he did have facial hair, but did not think his voice had deepened with puberty. He had been overweight and hypertensive since childhood.

On exam, he was obese but did not appear acromegalic or Cushingoid. There was a dense right central and superior temporal defect, and no detectable visual field abnormality on the left. Acuity was 20/15 on the left but he was unable to read an eye chart or count fingers with the right eye and left pupil did not react to light shone into right eye, consistent with afferent pupillary defect.

Endocrine testing revealed a 5pm cortisol of 6.3ug/dL (normal 5-15 ug/dL), an elevated prolactin at 465.9 ng/ml (normal <20), TSH 2.62 uIU/ml (normal 0.4-5.0), free T4 1.1 ng/dl (normal 0.9-1.8). Total testosterone was low at 44 ng/dL (normal 249-836 ng/dL).

A pituitary-protocol MRI with and without contrast revealed a 2.2 x 2.3 x 3.1 cm sellar mass with suprasellar extension that resulted in mass effect on the right prechiasmatic optic nerve, optic chiasm, and optic tract. The lesion was intrinsically T1 hyperintense and had a fluid layer on axial T2 imaging, suggesting a largely cystic component to the lesion (Figure 2).

Given the lab findings of a markedly elevated prolactin level and MRI findings of a large cystic tumor with significant optic nerve and chiasm compression, we had an interdisciplinary discussion about the next management steps of medical management versus surgery. Ultimately, given the cystic nature of the lesion and the significance of the patient's visual disturbance, we offered both options to the patient and he elected surgical decompression.

Four days after initial consultation, he was brought into the hospital for a transsphenoidal surgery for resection of the tumor. The tumor was found to be mostly cystic, with solid tumor along the left sella. Intraoperative MRI was obtained that did not show any obvious residual (Figure 3). His prolactin level on the morning of post-operative

Figure 1. Pre-operative visual field test demonstrating dense right eye junctional scotoma

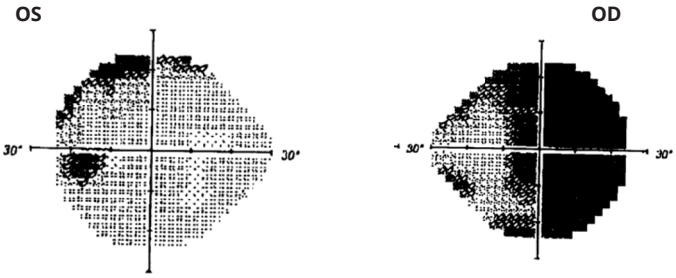
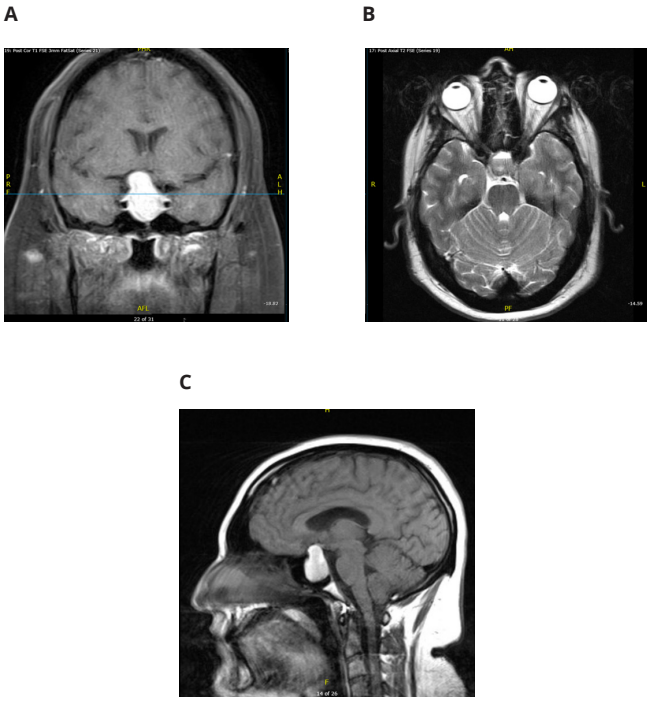


Figure 2.
A) Coronal post-contrast T1 sequence MRI showing homogenously enhancing mass with chiasmal compression.

B) Axial T2 sequence MRI demonstrates significant fluid level within the lesion.

C) Sagittal pre-contrast T1 sequence MRI showing inherent T1 hyperintensity of the lesion, consistent with cystic content.



day 1 was lower at 112.6 ng/mL, but remained abnormal. Vision in right eye improved to 20/50. His fasting morning cortisol was low at 6.3 ug/dL and he was discharged on prednisone 5mg daily.

At his 4-week post-operative endocrine visit the prolactin was 139.3 ng/mL. He was started on cabergoline 1mg weekly. He tolerated the medicine well and, after 3 months, prolactin down trended to 21 ng/mL. The

> *"medical therapy can be an effective and durable option, even in cases of large cystic tumors with chiasmal compression"*

dose was increased to 1.25mg weekly and his prolactin was normalized to 9 ng/mL. Testosterone increased spontaneously to 255 ng/dL, the lower limit of the normal range. His thyroid hormones remained normal and he was weaned off of prednisone at 2 months after surgery following a normal cosyntropin stimulation test. His right eye vision had improved to 20/30, and his afferent pupillary defect and visual field defect had both resolved. He denied headaches, and reported more energy and an increase in his physical activity.

Discussion

Prolactinomas are the most common of the functional pituitary tumors, comprising 51-66% of adenomas. Patients with these tumors typically present with hypogonadism, infertility or, in the case of macroadenomas, symptoms related to mass effect, such as visual field defects and headache. Medical management with dopamine agonists (DAs) has been the mainstay of treatment for several decades, with normalization of serum prolactin levels achieved in 75% of patients using bromocriptine and 85–90% using cabergoline.

Despite the effectiveness of DAs in achieving normal prolactin levels and shrinking the adenoma, with improvement in visual field defects within 24 hours in some patients, surgery for prolactinomas should be considered for a few scenarios. The most common role for surgery is in cases where patients are intolerant to medication, with side effects of nausea, dizziness, or even psychosis. Patients may also have a contraindication to DAs, such as psychiatric conditions. Another role for surgery includes drug resistance of the tumor—a failure to normalize prolactin and/or shrink tumor—that may be recognized with initial treatment or occur over time. Female patients with macroprolactinomas who are seeking pregnancy may be candidates for surgical resection over medical therapy given the need for expeditious restoration of fertility and the contraindication to taking DAs in pregnancy.

Largely cystic prolactinomas, as discussed above, were historically assumed to be resistant to DAs and therefore thought to be a surgical condition. Our group's research has shown that medical therapy can be an effective and durable option, even in cases of large cystic tumors with chiasmal compression. In this patient's case, we presented him with the data that DAs could be effective in treating his tumor, however the time course for shrinkage is variable, ranging from weeks to several months. Given his significant visual disturbance, our patient opted for surgery. After an informed, multidisciplinary discussion, patient preference is another reason for surgical intervention of prolactinomas, whether it is for visual concerns, as with our patient, or for the potential of avoiding or at least requiring a lower dose of DAs after significant tumor debulking.

References:

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2. Molitch ME. J Neurooncol. 2014; 117: 421-08
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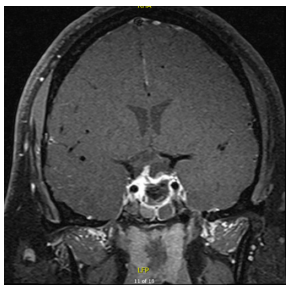
Figure 3.
A) Intra-operative coronal T1 post-contrast sequence MRI showing enhancement of pituitary stalk and gland within the right side of sella; no obvious remaining tumor

B) Intra-operative coronal T2 sequence MRI showing significant decompression of the optic chiasm

A



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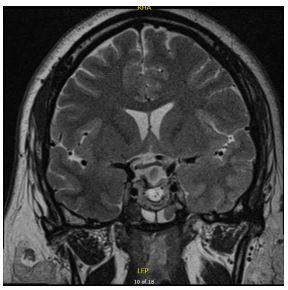

Research Studies Available

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	Quality of life Cross-sectional bone density study Study with a once a month, add-on therapy for those uncontrolled on highest dose of somatostatin analogues	Karen Pulaski Liebert, RN
Adults with active Cushing's Syndrome	Study with a twice daily oral therapy	Karen Pulaski Liebert, RN

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 (massgeneral.org/neuroendocrine) for more information about potential studies which may not be listed here.

Save the Date

MASSACHUSETTS GENERAL HOSPITAL AND HARVARD MEDICAL SCHOOL CME PRESENT

CLINICAL ENDOCRINOLOGY: 2019

April 3 – April 7, 2019
The Fairmont Copley Plaza
Boston, Massachusetts

For over 40 years this course has provided practicing endocrinologists and other healthcare providers with a comprehensive review and update of recent literature in clinical endocrinology. The faculty consists of staff endocrinologists at the Massachusetts General Hospital and Harvard Medical School as well as nationally-renowned guest lecturers, all selected for their teaching and clinical skills. A comprehensive syllabus is provided.

For additional information contact
Harvard Medical School
Department of Continuing Education

By mail
Harvard MED-CME, P.O. Box 825
Boston, MA 02117-0825

By telephone
617-384-8600

Registration and Program information are available at https://endocrinology.hmscme.com/

Save The Date

SPECIAL LECTURE

20th Annual Nicholas T. Zervas, M.D. Lectureship

Massachusetts General Hospital

Historic Ether Dome

Tuesday, May 21, 2019 at 12pm

Monica Gadelha, MD, PhD
Professor of Endocrinology at the Medical School of the Universidade Federal do Rio de Janeiro

For further information call Philip at 617-726-3870

Welcoming New Staff Member Dr. Mabel Toribio

Dr. Mabel Toribio earned her medical degree at the Johns Hopkins University School of Medicine. She then went on to complete her Internal Medicine residency training at the University of California, San Francisco; and her Endocrinology fellowship training at Massachusetts General Hospital. Dr. Toribio sees patients with neuroendocrine and pituitary disorders at the MGH Neuroendocrine and Pituitary Tumor Clinical Center and sees patients hospitalized at MGH through inpatient consultations. Additionally, she performs clinical research at MGH and provides teaching to medical students, residents, and other trainees at MGH and Harvard Medical School.

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SERVICES AVAILABLE

FACILITIES

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.

NEUROENDOCRINE AND PITUITARY TUMOR CLINICAL CONFERENCE

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.

SCHEDULING

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

The MGH Neuroendocrine and Pituitary Tumor Clinical Center Bulletin was supported in part by unrestricted educational grants from Crinetics Pharmaceuticals, Ionis Pharmaceuticals, and Sandoz. Other financial relationships may exist between these companies and The Massachusetts General Hospital.

Dr. Beverly MK Biller, Editor of the MGH Neuroendocrine and Pituitary Tumor Clinical Center Bulletin, is the primary investigator on research grants to the Neuroendocrine Unit from Ionis Pharmaceuticals, OPKO, Millendo Pharmaceuticals, NovoNordisk and Novartis and has occasionally consulted for Aeterna-Zentartis, Merck-Serono, Novartis, Ono, NovoNordisk, Pfizer, Strongbridge.

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