THE PITUITARY SOCIETY presents the

FIFTEENTH INTERNATIONAL PITUITARY CONGRESS

MARCH 29 - 31, 2017

Orlando, Florida

PROGRAM AND ABSTRACTS
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Welcome,

The Fifteenth International Pituitary Congress will present an exciting group of speakers expert in normal and disordered pituitary function. Our faculty includes distinguished clinicians and investigators, fellows in training, and basic scientists. As usual, we will present cutting edge in-depth topics that will permit our attendees to become familiar with the latest trends in pituitary endocrinology. The plenary format of the meeting is intended to facilitate maximum interaction and free exchange of ideas among participants and speakers.

This guide provides details of the scientific program as well as abstracts of the invited lectures, and those selected for Hot Topics and poster presentations.

Please note our partners who provide essential support for this meeting. We gratefully acknowledge their continued generosity and encouragement.

Welcome to two days of excellent science and companionship!

The Program Organizing Committee

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Niki Karavitaki, UK
Nicholas Tritos, USA
## Symposium Schedule

### Wednesday, March 29, 2017

**Opening Plenary**  
*Chairs: Andrea Giustina and Anthony Heaney*

- **7:00 PM**  
  Cortisol and Financial Decision Making  
  *Mark Gurnell*

- **7:30**  
  USP8 in Cushing Disease: Update  
  *Marily Theodoropoulou*

- **8:00**  
  In Memoriam

- **8:15**  
  Welcome Reception

### Thursday, March 30, 2017

**Continental Breakfast**

#### Pituitary Tumors: From Cell to Surgeon  
*Chairs: Eliza Geer and Maria Zatelli*

- **8:00**  
  Pituitary Lineage Specification: Roles of PROP1 and ISL1  
  *Sally Camper*

- **8:30**  
  A Novel Kinase Target for Pituitary Tumors  
  *Margaret Wierman*

- **9:00**  
  ErbB4 in Cushing Pathogenesis  
  *Hidenori Fukuoka*

- **9:30**  
  Determinants of Surgical Complications  
  *Brooke Swearingen*

- **10:00**  
  Coffee Break & Poster Session

#### Pituitary Dysfunction  
*Chairs: Andrea Glezer and Susan Samson*

- **10:30**  
  Dopamine Agonists & Impulse Disorders  
  *Niki Karavitaki*

- **11:00**  
  Drug-Induced Pituitary Dysfunction  
  *Nicholas Tritos*

- **11:30**  
  Oxytocin and Behavior Disorders  
  *Elizabeth Lawson*

#### Meet the Professor Lunch Sessions (Two 1 hour concurrent sessions)

- **12:00-2:00 PM**  
  Adult GH Replacement: Cost vs. Benefit  
  *Ariel Barkan, Andrew Hoffman*

  - Apoplexy: Conservative or Surgical Management?  
    *Adam Mamelak, John Wass*

  - Bilateral Adrenalectomy for Treating Cushing Disease  
    *Antoine Tabarin*

  - Growth Hormone, IGF-I and Cortisol Assay Technologies  
    *Martin Bidlingmaier, David Clemmons, Peter Trainer*

  - Management of Pituitary Tumors During Pregnancy  
    *Marcello Bronstein*

  - Pegvisomant vs. SRLs as First-line Acromegaly Therapy  
    *Aart Van der Lely*

#### Hot Topics  
*Chairs: Nienke Biermasz and Ken Ho*

- **2:15**  
  The Dual SSTR2/5 Specific Somatostatin Analog, AP102, Does Not Affect Glucose Metabolism in Diabetic ZDF Rats: A Comparative 14-day Infusion Study Versus Pasireotide  
  *Adrian Daly*

- **2:30**  
  Volumetric Changes of Whole Brain Gray Matter and White Matter in Patients with Cushing Disease Using Voxel-based Morphometry: A Prospective Study  
  *Lu Gao*

- **2:45**  
  Analysis of Expression of Sirtuin Gene Family in NFPA and Somatotropinomas  
  *Isabella Grande*
## Symposium Schedule

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<td>GnRH Pulse Frequency-dependent Regulation of FSHβ Expression is Mediated by Both Ga, and Gaq11 Proteins</td>
<td>George Stamatiades</td>
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**GROWTH HORMONE RESEARCH SOCIETY SYMPOSIUM**  
**Chairs: Gudmundur Johannsson and John Kopchick**

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<td>Yutaka Takahashi</td>
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<td>Effects of Growth Hormone on Brain Function</td>
<td>Fred Nyberg</td>
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<td>The Genetics of Stature: Unexpected Diversity</td>
<td>Jeffrey Baron</td>
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### FRIDAY, MARCH 31, 2017

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**PITUITARY TUMORS**  
**Chairs: John Carmichael and Lawrence Kirschner**

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<td>Maria Fleseriu</td>
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<td>9:00</td>
<td>Medical Treatment in Cushing Disease: Adrenal Focused</td>
<td>Richard Feelders</td>
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<td>9:30</td>
<td>Predictors of Therapeutic Response in Acromegaly</td>
<td>Monica Gadelha</td>
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<td>10:00</td>
<td>Should We be Measuring GH, IGF-I or Both in Following Acromegaly Patients?</td>
<td>Peter Trainer</td>
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**CRITERIA FOR ESTABLISHING PITUITARY TUMOR CENTERS OF EXCELLENCE (PTCOE)**

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<td>Developing Criteria for Pituitary Tumor Centers of Excellence</td>
<td>Felipe Casanueva</td>
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<td>Developing Criteria for Pituitary Tumor Centers of Excellence: Neurosurgical Perspective</td>
<td>Pietro Mortini</td>
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<td>11:40</td>
<td>Moderated Open Discussion: PTCOE</td>
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<td>12:30 PM</td>
<td>PRESIDENTIAL ADDRESS, AWARDS PRESENTATION &amp; BUSINESS MEETING</td>
<td>Andrea Giustina</td>
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<td>1:00</td>
<td>LUNCH</td>
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<td>2:00</td>
<td>CONGRESS ADJOURNS</td>
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OPENING PLENARY SESSION

Chairs: Andrea Giustina and Anthony Heaney

The Chairs have no relevant relationships to disclose.
Cortisol and Financial Decision Making

Mark Gurnell

Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, UK

The financial markets represent the largest and most intense competitive forum ever constructed. Here, according to classical economic theory, competition drives optimal allocation of capital to the projects with the highest returns, thereby promoting global prosperity. However, financial markets can be volatile and, as they cycle between ‘bull’ and ‘bear’ states, they occasionally overshoot to such an extent that they threaten the stability of the global economy.

Bull markets can morph into bubbles, in which investors display ‘irrational exuberance’ (an unrealistic assessment of expected returns, and of ability to predict the future); in contrast, bear markets may segue into financial crises, in which investors display ‘irrational pessimism’ (an almost complete aversion to risk). During bubbles and crashes investors typically react to price changes in a manner which is precisely the opposite to what economics would predict: the higher securities’ prices rise, the more investors buy them; the lower prices fall, the more investors shun them. Irrational exuberance and pessimism in our competitive and risk-taking behaviours thus contribute significantly to instability in global financial systems.

We have examined the potential for physiology-induced shifts in risk preferences to influence market stability on the world’s trading floors. Our findings show that when the amount of uncertainty, in the form of market volatility, increases, traders experience a sustained increase in cortisol levels. Using a double-blind placebo-controlled cross-over design, in volunteers who were incentivised to make financial choices, we have shown that a comparable, modest rise in cortisol levels is sufficient to render individuals significantly more risk averse.

Our findings point to an alternative model of risk taking in which risk preferences are not stable, but rather highly dynamic. Such a model might explain why the risk premium on equities rises and falls with volatility, and why the appetite for risk among the financial community seems to expand during a rising market, and contract during a declining one. Critically, if cortisol responds to increases in uncertainty and volatility, and volatility rises most strongly during a financial crisis, then risk taking may decrease just when the economy needs it most.

The author has no relevant relationships to disclose.

USP8 in Cushing Disease: Update

Marily Theodoropoulou

Neuroendocrinology, Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Ludwig Maximilians Universität München, Munich, Germany

The last two years have witnessed a renaissance in research surrounding the tumorigenic mechanisms leading to Cushing disease. The discovery of a somatic mutational hotspot in the gene encoding for the USP8 deubiquitinase by two independent groups brought the importance of protein stability in corticotroph pathophysiology back into focus. USP8 rescues growth factor and other cell surface receptors from lysosomal degradation, stabilizing them to the cell membrane and enabling their constitutive signaling. The most widely studied USP8 target is the epidermal growth factor receptor. EGFR is highly expressed in corticotroph tumors where it triggers aberrant ACTH synthesis and its pharmacological targeting with small molecule inhibitors was shown to reverse Cushing disease in animal models. We have shown that the USP8 mutants have higher deubiquitinase activity that retains an active EGFR, leading to increased ACTH synthesis. This talk will cover what we know about the role of the USP8-EGFR system as a trigger and target of corticotroph tumorigenesis and review the recent developments in the genetics of Cushing disease.

The author has no relevant relationships to disclose.
PITUITARY TUMORS: FROM CELL TO SURGEON

Chairs: Eliza Geer and Maria Zatelli

Eliza Geer has no relevant relationships to disclose; Maria Zatelli receives consulting fees from Ipsen and Novartis.
Pituitary Lineage Specification: Roles of PROP1 and ISL1

SA Camper\textsuperscript{1}, ML Brinkmeier\textsuperscript{1}, AH Mortensen\textsuperscript{1}, AZ Daly\textsuperscript{1}, MI Pérez Millán\textsuperscript{2}, SW Davis\textsuperscript{3}, P Gergics\textsuperscript{1}

\textsuperscript{1}University of Michigan Medical School, Ann Arbor, MI, USA; \textsuperscript{2}Institute of Biomedical Research, UBA-CONICET, Buenos Aires, Argentina; \textsuperscript{3}Department of Biological Sciences, University of South Carolina, Columbia, SC, USA

Pituitary cysts are common, non-neoplastic lesions that usually remain asymptomatic, but they can cause hypopituitarism, headache and visual problems if they enlarge. Rathke’s cleft cysts originate from the pituitary primordium and are typically characterized by keratin expressing, ciliated, columnar cells and squamous cells expressing P63. Little is known about the genetic origin of these lesions. We discovered that pituitary-specific disruption of the LIM homeodomain transcription factor ISL1 using Prop1-cre (Isl1Pitko) causes multifocal Rathke’s cleft cysts with 100% penetrance. Lesions are evident during embryogenesis and become progressively worse, enlarging with age. Given the clinical significance of Rathke’s cleft cysts and the availability of this novel animal model, we sought to understand the molecular mechanisms underlying the development of these lesions. We carried out RNA-Seq analysis on newborn Isl1Pitko mice and normal littermates, which revealed reduced TSH and LH beta subunit transcripts and massive up-regulation of genes typically expressed in cells secreting mucous and/or developing cilia. The cells lining the cysts exhibit strong expression of SOX2, a stem cell marker. Normally, SOX2 and ISL1 expression partially overlap in pituitary stem cell niches. We propose that ISL1 is required in pituitary progenitors to promote the transition to differentiation. Inhibition of this process in Isl1Pitko mice leads to cyst formation and transient hypopituitarism, as evidenced by transient growth insufficiency and reduced TSH production. Thus, ISL1 is important, together with several other transcription factors, for normal TSH production and growth.

Sally Camper has no relevant relationships to disclose.

A Novel Kinase Target for Pituitary Tumors

Margaret E. Wierman

University of Colorado School of Medicine, Denver Veterans Affairs Medical Center, Denver, CO, USA

Pituitary tumors are the most common brain tumor in veterans and in all persons occurring in 1 in 10,000 persons clinically, but in 1 in 5 at autopsy. The mechanisms underlying pituitary tumorigenesis are poorly understood. The classic oncogenes or tumor suppressor defects found in classic cancers are absent in human pituitary tumors and model systems are limited. Therefore, we developed a unique tissue bank of 600 human tumor and 150 normal pituitary samples. We have performed molecular profiling to further understand mechanisms of tumorigenesis, to identify biomarkers of disease progression and find novel targets for medical therapies for human tumors. Using a combined genetic and genomic screen of human tumor samples, mammalian sterile 20-like kinase 4 (MST4) was identified as a novel dysregulated kinase consistently upregulated at the transcript, mRNA and protein levels in most subtypes of tumors, and low to undetectable in normal human pituitary. We discovered that MST4 plays a unique role in driving tumorigenesis in a hypoxic microenvironment and identified its pituitary cell specific downstream effector pathways including PI3K/AKT, p38MAPK and hypoxia inducible factor 1 (HIF-1). The tumorigenic effects of MST4 were dependent on its kinase sequence and activity. A computational-based virtual screen of the SelleckChem kinase inhibitor library using the MST4 crystal structure identified hesperadin, initially identified as a putative Aurora kinase inhibitor, as a top candidate to abrogate MST4 actions. Hesperadin inhibited the MST4 kinase in the nanomolar range in a TR-FRET assay and abolished MST4 actions to protect pituitary tumor cells from hypoxia-induced apoptosis independent of its effects on Aurora kinase. Molecular profiling of human pituitary tumors provides insights into underlying pathogenesis and the identification and testing of new therapeutic targets for our patients.

The author has no relevant relationships to disclose.
ErbB4 in Cushing Pathogenesis

Hidenori Fukuoka
Division of Diabetes and Endocrinology, Kobe University Hospital, Kobe, Japan

Cushing disease is caused by ACTH-producing pituitary adenomas (ACTHomas). Although its tumorigenesis remains unclear, cell cycle dysregulation induced by abnormal p27/cyclin E/Rb pathway has been shown as a key pathogenic factor. EGF receptor (EGFR), an upstream of these pathways is frequently overexpressed in ACTHomas especially in USP8 mutated tumors. EGFR overexpression has been shown to induce its tumorigenesis, and its inhibition of tyrosine kinase activity suppresses both ACTH production and secretion. EGFR has been functionally interacted between its family member of ERBB, which includes ERBB2/HER2, ERBB3, and ERBB4. To investigate the function of these ERBB in ACTHomas, we tested the effect of pan-ERBB tyrosine kinase inhibitor (TKI), canertinib, to surgically resected ACTHoma cells and compared the effect of EGFR specific TKI, gefitinib. Gefitinib suppressed POMC synthesis in EGFR expressed ACTHomas (68%, p <0.01), but not in EGFR negative tumors. Intriguingly, canertinib suppressed POMC expression in gefitinib resistant tumors (87%, p <0.001). This effect was more apparent in ERBB4 overexpressed ACTHomas (p <0.05). Thus, we focused on the ERBB4 function in ACTHomas.

ERBB4 overexpression has been shown in breast cancer, medulloblastoma, and colon cancer, and its function is mediated by two separate pathway; signaling pathway (MAPK, PI3K), and a function as transcriptional co-factor (cleaved intracellular domain). We tested the ERBB4 expression levels and its clinical relevance in patients with Cushing disease. All ACTHomas expressed ERBB4 and its expression levels were negatively associated with Knosp grade (p =0.01). ERBB4 has 2 functionally different isoforms of intracellular domain, namely CYT1 and 2. In medulloblastoma, CYT2 has been shown to suppress tumor proliferation. In ACTHomas, CYT2 isoform was predominantly expressed. This expression pattern was obviously different from that in normal pituitary. These support our present data that ERBB4 overexpression was negatively correlated with Knosp grade in ACTHomas. In conclusion, ERBB4 expression levels are related to canertinib sensitivity, and tumor invasiveness in ACTHomas.

The author has no relevant relationships to disclose.

Determinants of Surgical Complications

Brooke Swearingen
Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Transsphenoidal surgery remains a safe and effective treatment for many pituitary adenomas. Surgical complications are uncommon, but are in part determined by surgical experience, patient anatomy and tumor configuration, underlying disease, and surgical technique. Post-operative endocrine complications – SIADH, DI and hormone insufficiency - require close collaboration between the surgeon and endocrinologist. We will review the literature regarding these determinants of surgical complications and discuss strategies for their avoidance and management.

The author has no relevant relationships to disclose.
PITUITARY DYSFUNCTION

Chairs: Andrea Glezer and Susan Samson

The Chairs have no relevant relationships to disclose.
Dopamine Agonists and Impulse Disorders

Niki Karavitaki

Institute of Metabolism and Systems Research, University of Birmingham & Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK

Dopamine agonists (DA) are the treatment of choice for patients with prolactinomas and are generally safe, effective and well tolerated. However, a link between their use and the development of impulse control disorders (ICD) has been well recognised in the field of neurology, and evidence for a similar effect in endocrine patients is emerging. The ICDs are defined as “failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or others”. They include, but are not limited to, problem gambling, hypersexuality, compulsive eating, compulsive shopping and “punding”. The mechanism of action behind ICDs is probably an interaction between the DAs and the D3 receptors in the mesolimbic system, known to be responsible for the process governing behaviour, pleasure and addiction. The relevant published literature on patients with prolactinoma includes case reports or retrospective studies limited by small sample sizes and shortcomings in experimental design. ICDs might affect both sexes of any age, at any stage of their treatment, usually but not necessarily associated with a high dose of DA. Unlike other physical side effects, patients may not associate ICDs with their medication or neglect to mention them at follow-up out of embarrassment. Given the potential to cause severe mental, social, and financial consequences for the patient, it therefore, falls to the endocrinologist to warn patients to be vigilant for ICDs prior to initiation of DAs and actively enquire about them at follow-up appointments. Patients’ families who often appreciate behavioural changes prior to the patient themselves, should also be involved in this process. Prospective, randomised controlled trials are required to fully assess the relationship between DAs and ICDs in patients with prolactinoma.

The author has no relevant relationships to disclose.

Drug-Induced Pituitary Dysfunction

Nicholas A. Tritos

Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

A plethora of pharmacologic agents have been reported to have adverse effects on pituitary function. However, pertinent data often represent findings from animal studies, reports of acute effects in humans, case reports or series. It should be noted that high quality data are rather sparse in this area.

The aim of this presentation is to succinctly review primarily chronic effects of select pharmacologic agents on pituitary function, wherein the action is unintentional and considered adverse. Adverse events of medical therapies used to treat pituitary disorders will not be considered herein. Case studies will be utilized in order to highlight the actions of several agents on aspects of pituitary function, including the effects of an herbal extract with glucocorticoid properties, opioid-induced pituitary dysfunction, medication-induced hyperprolactinemia, androgen-induced hypogonadism and infertility, and immune checkpoint inhibitor-related hypophysitis.

Such observations serve to remind us that the effects of medications can be pleiotropic. Some drugs may inadvertently influence pituitary function as a consequence of “off target” effects. In other cases, these actions may represent an extension of their major pharmacologic properties. High quality data are needed in order to characterize the prevalence of pituitary endocrinopathies in association with diverse pharmacologic agents and the magnitude of associated morbidity, establish predictors of endocrine dysfunction in patients at risk and fully elucidate the underlying pathophysiological mechanism(s). A high index of suspicion and a multidisciplinary approach are needed in order to detect and manage such adverse events in a timely manner towards optimizing patient outcomes.

The author’s institution receives directed research support from Ipsen, Novartis, Novo Nordisk, and Pfizer.
Oxytocin and Behavior Disorders

Elizabeth Lawson

Harvard Medical School, Director, Interdisciplinary Oxytocin Research Program, Neuroendocrine Unit, Massachusetts General Hospital, Boston, MA, USA

Oxytocin, produced in the hypothalamus and secreted directly into the brain as well as to the peripheral circulation via the posterior pituitary, has a range of important physiologic effects including the regulation of eating behavior and metabolism. Preclinical studies have consistently demonstrated that exogenous oxytocin reduces body weight by inhibiting food intake, particularly of palatable foods, and increasing energy expenditure. Furthermore, oxytocin is anabolic to bone. Oxytocin also has anxiolytic, antidepressant, and pro-social properties. We have investigated oxytocin in two human models at extremes of eating behavior: (1) the low-weight eating disorder anorexia nervosa (AN), and (2) obesity. In women with AN, we have found that serum oxytocin levels are low and associated with clinical characteristics, including severity of psychological symptoms (anxiety and depressive symptoms, social-emotional impairment) and extent of bone loss. We speculate that oxytocin levels are suppressed as an adaptive response to chronic starvation in AN in order to increase the signal to eat and conserve limited resources, with negative secondary effects. While oxytocin could be considered as a treatment for these psychological and bone complications in AN, the potential of oxytocin to do harm by increasing the energy deficit in this population must be considered. In contrast, oxytocin represents a potential novel neuroendocrine therapy for obesity. In men, we have shown that a single dose of intranasal oxytocin reduces food intake, particularly of fats, increases fat utilization, and improves insulin sensitivity, similar to findings in animal models. Using fMRI, we have demonstrated two potential mechanisms for oxytocin effects on food intake: (1) reduced activation of reward-related food motivation neurocircuitry; and (2) increased activation and connectivity of inhibitory control brain regions and reduced impulsive behavior. Further research will be important to define the underlying mechanisms and establish the efficacy and safety of chronic oxytocin administration in the treatment of obesity.

The author is on the Scientific Advisory Board of OXT Therapeutics, Inc.
Adult GH Replacement: Cost vs. Benefit

Ariel Barkan1,2 and Andrew Hoffman3

1Endocrinology and Metabolism, 2Neurosurgery, University of Michigan, Ann Arbor, MI USA; 3Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA

With the abundant availability of recombinant human growth in the late 1980s, a syndrome of adult GH deficiency syndrome was recognized and defined. Most of these patients were panhypopituitary patients who had pituitary or hypothalamic tumors, and it was noted that despite corticosteroid, sex steroid and thyroid hormone replacement, many patients complained of decreased energy, lassitude and changes in body composition. It was shown that panhypopituitary patients had a decreased life expectancy, with increased cardiovascular, bone and oncologic diseases. Numerous studies have shown that GH replacement therapy can treat many of the symptoms of GH deficiency in these patients. Nonetheless, most patients with GH deficiency are not given GH replacement therapy, and there remain substantial controversies regarding the diagnosis, costs and true benefits of this therapy. In this Meet the Professor Session, Drs. Barkan and Hoffman will debate the relative merits and risks of GH therapy for adult patients with hypopituitarism.

Ariel Barkan has no relevant relationships to disclose; Andrew Hoffman receives consulting fees from Gene Science, Genexine, Pfizer, and Versartis.

Apoplexy: A Rationale for Surgical Management

Adam N. Mamelak

Pituitary Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Rationale: Pituitary apoplexy (PA), generally defined as acute hemorrhagic infarction of a pituitary adenoma, occurs in approximately 1-2% of all adenomas. Clinical symptoms are largely due to rapid expansion of a sellar mass caused by necrosis and hemorrhage. Clinical management is aimed at reversal of neurological and endocrine symptoms. For many years PA was considered a neurosurgical emergency, with intervention recommended within 48-72 hours of presentation. More recently, medical management without surgery has been advocated by several groups, based on data suggesting that patients treated with or without surgery have similar outcomes. Method: We present two cases, both presenting with hypopituitarism and visual loss that serve as a springboard to review the medical literature supporting surgical intervention. One case was operated upon early with full recovery of vision and hormone status. The other was initially managed medically with delayed surgery, and a poor outcome. Results: Several series comparing surgical outcomes with medical management generally support the conclusion that surgical intervention is more effective than medical management alone for cases with visual defects that either fail to recover in a few days, or worsen. They further support the view that surgical intervention is preferred for patients with diminished levels of consciousness, hydrocephalus due to mass effect, and subarachnoid hemorrhage. There is an 11% recurrence rate of adenomas in patients with PA, which may be reduced by surgical intervention. In the United States, the medico-legal climate remains an important consideration as well, often prompting earlier and more aggressive surgical interventions. Conclusions: Substantial evidence supports the central role of surgery in the treatment of PA, although conservative therapy is appropriate in selected situations. Established guidelines serve as a useful tool for the clinician in deciding between these two approaches. Ultimately, an integrated medical and surgical rationale is required for the optimal management of pituitary apoplexy.

The author has no relevant relationships to disclose.
Bilateral Adrenalectomy for Treating Cushing Disease

Antoine Tabarin

Department of Endocrinology, University Hospital of Bordeaux, Bordeaux, France

The first line treatment for Cushing disease is transsphenoidal surgery (TSS). However, despite being performed by experienced surgeons, the long-term remission rate of CD using TSS is around 60 - 70%. Although bilateral adrenalectomy (BLA) is no longer the first-line treatment for CD, it continues to play a valuable role in the treatment of patients with persistent or recurrent hypercortisolism after TSS. BLA is a safe treatment modality when performed with a laparoscopic approach but carries a median morbidity rate around 15%. The specific advantages of BLA include an immediate effective control of hypercortisolism associated with a rapid improvement in Cushing-co-morbidities and quality of life. Aside from the need for life-long steroid substitutive therapy, the complications of BLA include the development of adrenal crisis, occult glucocorticoid over-replacement by patients and re-growth of the pituitary corticotropic adenoma remnant (so-called “Nelson’s syndrome”). Alternative therapeutic options in patients with persistent or recurrent hypercortisolism after TSS include repeat TSS, radiotherapy, medical therapy and chemical adrenalectomy. Similarly to BLA, all these options have pros and cons. Therefore, the treatment of these difficult cases should be discussed within an experienced multidisciplinary team and shared with patients allowing a case-by-case therapeutic strategy. The rate of persistent Cushing-co-morbidities and life expectancy following remission of Cushing disease may be related to the duration of exposure to hypercortisolism. An important issue is whether BLA should still be considered as an ultimate option after TSS and medical therapies have failed. All these aspects will be discussed during the session using case reports.

The author has no relevant relationships to disclose.

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Pituitary Apoplexy: Diagnosis and Management

John Wass1,2

1 University of Oxford, 2 Department of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK

Pituitary apoplexy is an uncommon emergency. It presents often with sudden thunder clap headaches and requires multidisciplinary team involvement. This includes an experienced neurosurgeon, endocrinologist, radiologist – the pituitary multidisciplinary team.

Urgent treatment should be given often involving steroids (after a blood cortisol has been taken). Assessment includes neurological signs which if severe may merit urgent surgery.

Surgery in these circumstances is controversial but certainly if there is profound neurological sequela including third, fourth or sixth cranial nerve problems and optic nerve problems, early surgery should be recommended to decompress the neural pathways.

Ongoing studies looking to see whether urgent surgery improves neurological outcomes in borderline cases are underway.

Patients who have had pituitary apoplexy require long-term follow up because pituitary tumours which commonly cause this problem can recur.

The author has no relevant relationships to disclose.
Growth Hormone, IGF-I and Cortisol Assay Technologies

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Martin Bidlingmaier receives consulting fees from DiaSorin and IDS.

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Disclosures, if any, will be provided prior to the presentation.

IGF-I Assay Update: Clinical Utility and Assay Performance

David Clemmons
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A 2010 workshop made several recommendations regarding the quality and performance of growth hormone (GH) and IGF-I assays and there has been substantial progress toward their successful execution. Two site sandwich assays have been improved in several respects. The recombinant standard 02/254 is now utilized by several reference laboratories and there is more widespread use of serum as a matrix. Several labs have followed recommendations regarding IGF binding proteins and demonstrated that their assay is free of binding protein interference. Some laboratories have published normative data obtained from large numbers of subjects including children. Utilization of these standardized reference populations has significantly improved diagnostic accuracy. Published comparisons between assays from different reference laboratories have shown that discrepancies are due to use of different calibrators or non-comparable normal reference populations. When these parameters are standardized the differences narrow. A major development has been the widespread use of mass spectrometry assays. These essays are quite accurate and free from binding protein interference. However they still rely on pre-analysis sample concentration or enzymatic digestion, which is subject to variability. Nevertheless these assays provide a qualitatively different method for assessment of accuracy and reproducibility. Due to these issues clinical utilization of the results of both types of assays make it difficult to use IGF-I values to diagnose the presence of GH deficiency or assess the effects of treatment in acromegaly when comparing IGF-I to the results of GH testing. Although not in widespread clinical use the development of the Kira assay has been useful for clinical research and for raising questions as to the validity of clinical conclusions that can be drawn from IGF-I measurements obtained using other techniques. Progress in each of these areas is encouraging and suggests that future improvements will enable attainment of the goal of reproducible assays that accurately reflect GH secretory status.

The author has no relevant relationships to disclose.
Management of Pituitary Tumors During Pregnancy

Marcello D. Bronstein

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Pituitary tumors, usually adenomas, account for about 10–15% of all intracranial tumors, and often affect patients of reproductive age. Their low fertility rate is generally due to gonadotrophic axis impairment resulting from hormonal hypersecretion and/or tumor mass effect. Advances in surgical and medical treatment of pituitary adenomas and induction of ovulation procedures have turned pregnancy into a reality for women harboring pituitary adenomas. Nevertheless, the pregnancy strategy and follow-up should be judiciously performed to minimize the risks for both mother and fetus. Women with prolactinomas account for most cases of pregnancies with pituitary tumors. Medical therapy with dopamine agonists (DA) is the treatment of choice for most patients bearing micro or macrolactinomas, bromocriptine still representing the more indicated drug. Cabergoline, however, does not seem deleterious. The DA should be withdrawn at pregnancy diagnosis for microprolactinomas, intrasellar macroadenomas or expansive macroadenomas that shrank within sellar boundaries. In case of tumor expansion during pregnancy, DA reintroduction is the first approach to be done. Pituitary surgery is reserved for women with prolactinomas resistant to DA or with potential risk of mass-effect not controlled by DA therapy. Concerning acromegaly, Cushing’s disease and clinically nonfunctioning pituitary adenomas, surgery before conception is the gold standard treatment. Patients with uncontrolled acromegaly or Cushing’s disease present high risk of materno-fetal morbidities. In acromegaly, medical treatment with somatostatin receptor ligands should be discontinued, preferably prior to conception, with reintroduction during pregnancy, if needed. Of note, some patients present normalization of IGF-1 levels during pregnancy, without the need for therapeutic intervention. Regarding patients with Cushing disease with surgical failure, medical treatment with metyrapone or ketoconazole or even bilateral adrenalectomy should be considered for severe cases.

The author has no relevant relationships to disclose.

This presentation will include discussion of product(s) that are unlabeled (off-label) for use as approved by the FDA or by the equivalent regulatory authority in the country in which the studies or trials were performed.

Pegvisomant vs. SRLs as First-line Acromegaly Therapy

AJ van der Lely

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A personalized approach of the acromegaly will assist the treating physician to discuss with the patient which medical treatment option is the best. When tumor size is the problem, available data clearly indicate that SRLs are the first choice, but when active disease is the issue, they might consider to start with pegvisomant (PEGV). Due to their mode of action, SRLs not only decrease GH levels but also make the liver GH resistant via direct and indirect mechanisms. Therefore, in acromegaly patients that have a normal IGF-I concentration during long-term SRL treatment (so who considered to be biochemically controlled), GH levels are relatively high compared to the GH concentrations that can be found in surgical treated patients with normal postoperative IGF-1 levels.

On the other hand, PEGV decreases GH actions that results in in several tissues, but the concentrations of PEGV needed to normalize serum IGF-1 are high compared to the ones that are needed to inhibit lipolysis and renal hyperfiltration. This implies that PEGV will induce a biochemical state of GH deficiency in several tissues before IGF-1 levels drop into the normal range.

So, SRLs & pegvisomant have clear different effects on metabolism that are tissue dependent. This implies that IGF-I levels alone might not give enough information on the metabolic status and level of disease activity during medical treatment, i.e., we need more & better (tissue-specific) parameters.

The author receives consulting fees from Ipsen, Novartis, and Pfizer.
HOT TOPICS

Chairs: Nienke Biermasz and Ken Ho

The Chairs have no relevant relationships to disclose.
The Dual SSTR2/5 Specific Somatostatin Analog, AP102, Does Not Affect Glucose Metabolism in Diabetic ZDF Rats: A Comparative 14-Day Infusion Study Versus Pasireotide

Adrian F. Daly 1, Mark Sumeray 2

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Somatostatin analogs (SSA) acting through SSTR2 like octreotide and lanreotide are a mainstay of acromegaly and neuroendocrine tumor treatment. Pasireotide, a newer compound acting mainly through SSTR5 and SSTR2, is used to treat Cushing disease and standard SSA-resistant acromegaly but has diabetogenic effects in animals and man. AP102 is a new SSA that has balanced sub-nanomolar affinity at SSTR2/SSTR5. We characterized the effect of AP102 versus pasireotide on glucose control in male ZDF rats, a standard diabetes model.

Diabetic ZDF rats were implanted with subcutaneous pumps containing AP102, pasireotide (3µg/kg/day) or vehicle, for 14 days. Fasting blood glucose was measured at baseline and on days 4 and 11. An oral glucose tolerance test (OGTT) was performed at baseline and on days 8 and 14. Water and food intake was measured daily.

All 3 groups were diabetic at baseline. Throughout the study the pasireotide group had significantly increased food and water intake as compared with vehicle and AP102 groups (P<0.001). AP102 did not differ from vehicle in terms of food/water intake, fasting glucose or OGTT responses. In contrast, pasireotide treated ZDF rats had significantly increased glucose AUC on OGTT as compared with vehicle (p<0.05) and AP102 (p<0.01) on day 14. There were no significant inter-group differences in terms of insulin, glucagon and GLP-1.

Unlike pasireotide, AP102 did not impair glucose control in diabetic rats, despite having high SSTR2/5 binding affinity. AP102 could represent a significant improvement over existing compounds if confirmed in human studies.

Adrian Daly is a consultant for Amryt Pharmaceuticals; Mark Sumeray is an Amryt Pharmaceuticals employee.

Volumetric Changes of Whole Brain Gray Matter and White Matter in Patients with Cushing Disease Using Voxel-Based Morphometry: A Prospective Study

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Objective: The aim of the study was to prospectively assess the changes of whole brain gray matter and white matter volume in patients with Cushing disease using voxel-based morphometry (VBM). Besides, the correlation between abnormal brain volume and Scheltens score, Montreal Cognitive Assessment (MoCA) scale, course of disease and other possible risk factors were also evaluated. Methods: Twenty-one patients with Cushing disease, confirmed by pathology, were consecutive enrolled in the study from Peking Union Medical College Hospital. Nineteen sex and age matched healthy individuals were selected as controls. The whole brain three-dimensional structure imaging was evaluated using VBM method, which is based on satirical parametric mapping (SPM) 12 software. The whole brain gray matter and white matter volume differences between the two groups were analyzed accordingly. The Spearman rank test was used to analyze the correlation between abnormal brain volume and Scheltens, MoCA score and course of disease in patients with Cushing disease. This study was approved by the Ethical Committee of PUMCH. Results: Compared with control group, the cerebral gray matter volume was decreased in multiple regions in the group with Cushing disease. The changes in bilateral frontal lobe, temporal lobe and limbic lobe were statistically significant (p < 0.05). The atrophy volume of gray matter was positively correlated with the course of disease (p < 0.05) in certain cerebral regions, including left temporal lobe, superior temporal gyrus and temporal gyri. Conclusion: Our study confirmed the whole brain atrophy in patients with Cushing disease using VBM method. Quantitative analysis of the reduced gray matter volume demonstrated that the left temporal lobe atrophy volume and the course of disease were positively correlated. Thus, we should pay more attention to the early diagnosis and treatment of Cushing disease, in order to reduce the occurrence of severe brain atrophy.

The authors have no relevant relationship to disclose.
Analysis of Expression of Sirtuin Gene Family in NFPA and Somatotropinomas

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Sirtuins 1-7 (SIRT) are a conserved family of deacetylases that regulate lifespan in different organisms and are involved in different tumorigenic processes. Loss of sirtuins expression is known to contribute to genomic instability and we speculated that these proteins could play a role in the pituitary tumorigenesis. We investigated SIRT1, 2, 4, 5, 6 and 7 expression of the in pituitary adenomas, relating such expression to clinical, laboratory and imaging characteristics of these tumors. For this, 23 nonfunctioning pituitary adenomas/NFPA and 37 somatotropinomas were evaluated. All specimens were macroadenomas and invasiveness was observed in 28 tumors (18 somatotropinomas and 10 NFPA). Tumor mRNA levels were assessed by SYBR green relative quantification. The categorical data were expressed as percentages and compared by Chi-square test using Sigma Stat. P<0,05 was considered statistically significant. This study was approved by the local Ethics Committee. We observed SIRT2 low expression in approximately 70% of all neoplastic samples. Already the SIRT4 and SIRT7 was showed underexpressed in NFPA in 40,6% and 65,6%, respectively. SIRT1 and SIRT4 underexpression was strongly correlated with NFPA (p=0,018). In addition, overexpression of SIRT1 was remarkable in somatotropinomas (46.9%). Interestingly, SIRT1 promotes replicative senescence, a mechanism that has been recently suggested as a possible explanation for the usually benign behavior of pituitary tumors, at least in somatotropinomas. SIRT5 and SIRT6 was normal in more than 50% for both subtypes. However, there was no significant association between sirtuins gene expression with the patients’ characteristics. In conclusion, our results suggested that loss of expression of sirtuins could be involved in the NFPA tumorigenesis. However, further studies are needed to determine the specific role of these proteins in pituitary neoplastic transformation.

The authors have no relevant relationships to disclose.

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GnRH Pulse Frequency-dependent Regulation of FSH<sub>β</sub> Expression is Mediated by Both G<sub>αs</sub> and G<sub>αq/11</sub> Proteins

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The pulsatile release of GnRH activates signal transduction cascades in the pituitary gonadotrope to control the synthesis and secretion of FSH and LH. FSH contains a distinct FSH<sub>β</sub> subunit, preferentially stimulated at low (every 2 h) rather than high (every 30 min) GnRH pulse frequencies. GnRH binds to its receptor, GnRHR, which interacts with heterotrimeric G proteins to initiate downstream signaling. It has been demonstrated that GnRH stimulates both G<sub>αR</sub>-associated Gas and Gαq/11-mediated signaling pathways in the murine LbT2 gonadotrope-derived cell line. To identify the role of Gas and Gαq/11 proteins in the GnRH pulse frequency-dependent regulation of Fshb expression, knockdown (KD) of Gas and Gαq/11 by lentiviral shRNA transduction was performed in LbT2 cells. Effective KD efficiency was demonstrated by western blot analysis. LbT2 cells transduced with scrambled, Gas, or Gαq/11 shRNA were perfused and treated with pulsatile GnRH at varying pulse frequencies (every 30 min or 2 h) for 20 h. As expected, LbT2 cells transduced with a scrambled control shRNA showed a GnRH pulse frequency-dependent pattern of induction of Fshb expression, with significantly greater induction at low than at high GnRH pulse frequency, compared to cells perfused with media only. In Gas KD cells, the induction of Fshb mRNA levels was reduced at low GnRH pulse frequency to an extent such that the pulse frequency-dependent pattern of induction was lost. On the other hand, in Gαq/11 KD cells, the induction of Fshb mRNA levels was significantly reduced at high GnRH pulse frequency. In conclusion, these findings suggest that Gas-stimulated pathways mediate Fshb expression in response to pulsatile GnRH at low GnRH pulse frequencies, whereas induction of Fshb at high frequencies of pulsatile GnRH occurs via Gαq/11-stimulated pathways. These findings offer further insight into the mechanisms by which the gonadotrope decodes the pulsatile GnRH signal to regulate FSH.

The authors have no relevant relationships to disclose.
GROWTH HORMONE RESEARCH SOCIETY SYMPOSIUM

Chairs: Gudmundur Johannsson and John Kopchick

The Chairs have no relevant relationships to disclose.
Growth Hormone and the Liver

Yutaka Takahashi
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Classical somatomedin hypothesis advocated that GH stimulate IGF-I production in the liver and the IGF-I exerts growth-promoting activity. Thus it has been considered that main role of liver was producing IGF-I. However, accumulating evidence indicate that GH and IGF-I plays an essential role in the liver and that liver is one of the important target tissue for these hormones.

We have demonstrated that patients with adult growth hormone deficiency (AGHD) demonstrate an increased prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH), and GH replacement therapy restores these conditions (Gastroenterology 2007 132 938, EJE 2012 167 67, GH & IGF Res 2014 24 174, Endocr J 2012 59 955). NASH is a serious disease because it causes inflammation and fibrosis and progresses to liver cirrhosis and hepatocellular carcinoma. Therefore, it is necessary to pay attention in patients with AGHD who present with NASH.

Regarding the underlying mechanisms, it has been reported that GH has an anti-lipogenic activity in hepatocytes. Interestingly, not only GH but also IGF-I reverses NASH in GH-deficient rat model, suggesting a pivotal role of IGF-I in the liver (BBRC 2012 423 295). Recently, we demonstrated that IGF-I improves oxidative stress and mitochondrial dysfunction, which are the causal factors of NASH, in hepatocyte. In addition, hepatic stellate cells, which are key player in the development of fibrosis, express IGF-I receptor, and IGF-I induces cellular senescence and inactivates these cells, thus limits fibrosis (Sci Rep 2017 in press). We have also shown that IGF-I drastically improves inflammation and fibrosis in general NASH and cirrhotic animal model, suggesting that IGF-I may be applicable for the treatment of general NASH.

The author has no relevant relationships to disclose.

Effects of Growth Hormone on Brain Function

Fred Nyberg
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Growth hormone (GH) and its mediator insulin-like growth factor-1 (IGF-1) are shown to induce profound effects on the central nervous system (CNS). Targets for these hormones have been identified and characterized in various regions of the CNS. Also, a number of clinical and preclinical studies have demonstrated that GH may elicit significant improvements in a variety of psychological capabilities. The hormone has been attributed a role in the repair of various brain deficits. For instance, in GH deficient (GHD) patients suffering of many disabilities the hormone has been shown to elicit effects leading to increase quality of life. Beneficial effects of GH on certain CNS-related functions, including alertness, cognition and wellbeing have thus been reported. Also, in GHD children significant improvements have been observed in several behaviors related to CNS. In experimental animals both GH and IGF-1 have been found to enhance cognition function. Moreover, earlier studies indicated that chronic opiates inhibit cell growth and trigger apoptosis, which in turn impairs cognition in both human and rodents. We have reported that GH reverses opiate-induced apoptosis in murine primary hippocampal cells. All these findings suggest that the hormone is capable of preventing or even repairing drug-induced damage to brain and thereby restore cognitive function. This presentation highlights our ongoing studies on GH replacement in both animals and human subjects with drug-induced cognitive deficits. It describes studies on human subjects with opioid-induced cognitive disabilities, who responded to GH treatment as confirmed by cognitive tests as well as MRI analysis. Regarding routes of GH administration a describing that in experimental animals the hormone may be administrated by nanowire delivery to attenuate damage from spinal cord injury and we also describe a new route of GH administration through gene therapy. Thus, a recombinant AAV vector encoding the GH gene was constructed and applying immunological techniques we observed that both GH and IGF-1 were present and measurable in brain areas related to cognition.

The author has no relevant relationships to disclose.
The Genetics of Stature: Unexpected Diversity

Jeffrey Baron

Section on Growth and Development, National Institutes of Health, Bethesda, MD, USA

Powerful, new, unbiased tools have recently been developed to investigate the genetic control of childhood growth. These approaches include genome-wide association studies and exome sequencing. Concomitantly, cell culture, organ culture, and animal studies have helped elucidate the mechanisms regulating growth plate chondrogenesis, the biological process that drives height gain. Taken together, findings from these studies have challenged the paradigm that the GH-IGF-I axis is the central system regulating childhood growth. Instead, they suggest that the GH-IGF-I axis is just one of many regulatory systems that control chondrogenesis in the growth plate, and therefore linear growth. Normal growth in children depends on multiple hormones, paracrine factors, extracellular matrix molecules, and intracellular proteins that regulate growth plate chondrocytes. Consequently, the primary genetic defects responsible for short and tall stature lie scattered throughout these many regulatory systems. Similarly, genome-wide association studies have revealed that the normal variation in height appears to be due to genes that affect growth at the growth plate through a wide variety of mechanisms. Often sequence variants in genes that affect growth plate chondrogenesis can produce a broad phenotypic spectrum. For example, homozygous loss-of-function mutations may cause a skeletal dysplasia, heterozygous loss-of-functions mutations in the same gene may present as isolated monogenic short stature, common polymorphisms in the gene may contribute to polygenic short stature, and gain-of-function mutations may result in tall stature.

The author has no relevant relationships to disclose.
PITUITARY TUMORS

Chairs: John Carmichael and Lawrence Kirschner

John Carmichael receives honoraria from Ionis, Novartis, and Pfizer; Lawrence Kirschner receives consulting fees from Corcept.
Medical Treatment in Cushing Disease: Pituitary Focused

Maria Fleseriu

Northwest Pituitary Center, Departments of Medicine and Neurological Surgery, Oregon Health & Science University, Portland, Oregon, USA

Medications used for treatment of Cushing Disease (CD) are classified into three groups: pituitary-directed drugs, adrenal steroidogenesis inhibitors and glucocorticoid receptor blockers. We will focus here on pituitary-directed therapies.

Corticotroph pituitary adenomas often highly express dopamine 2 receptor (D\textsubscript{2}R) and somatostatin receptor subtype 5 (sst\textsubscript{5}). Pasireotide, a multiligand somatostatin receptor ligand (SRL), is the first pituitary-directed agent to be approved for use in CD as a twice-daily subcutaneous injection. In the initial phase III study, 14.6% and 26.3% of patients on 600 µg and 900 µg BID, respectively had normal UFC after 6 months and tumor shrinkage was also observed. Late night salivary cortisol (LNSC) decreased during treatment too; interestingly, there was only a moderate correlation between individual patient LNSC and UFC values. Hyperglycemia-related adverse events occurred in 79% of patients treated for 2 years, therefore patients should be closely monitored for hyperglycemia and appropriate treatment initiated.

There are no clear-cut predictive factors for biochemical or clinical response, but patients with mild Cushing might have better biochemical outcomes. Additionally, it has been suggested that presence of USP8 mutations may predict favorable responses to pasireotide. On another note, patients with aggressive ACTH-secreting tumors have been observed to have atypical paradoxical responses to pasireotide with significant UFC increase and/or escape. Results from a recent phase III study showed that monthly pasireotide LAR effectively lowers UFC levels with a tolerability profile similar to the twice-daily subcutaneous formulation. In patients with milder disease, 52% (13/25) of patients in both 10 mg and 30 mg monthly groups achieved UFC normalization.

Cabergoline therapy has achieved varied results in both prospective and retrospective studies. About 20-25% of CD patients are responders to cabergoline in retrospective studies; neither baseline UFC, nor prolactin levels could predict the response.

Promising new molecular targets have been identified, including retinoic acid receptors, cyclin-dependent kinases and epidermal growth factor receptor (EGFR). These involve pathways that have been linked to the regulation of pro-opiomelanocortin expression, ACTH secretion, and tumor growth. Retinoic acid has been studied in 2 small prospective studies with UFC normalization in a quarter of patients with CD. R-roscovitine inhibits human pituitary corticotroph tumor ACTH by targeting the cyclin E/E2F1 pathway. After initial studies in mouse models, R-roscovitine has been shown to also inhibit human corticotroph tumor POMC and Tpit/Tbx19 transcription with decreased ACTH expression. A phase II study with this drug in patients with CD is ongoing. In an allograft mouse model, the C-terminal HSP90 inhibitor silibinin showed anti-tumorigenic effects, partially reverted hormonal alterations, and alleviated symptoms. Gefitinib, an EGFR inhibitor, is being studied in patients with USP8-mutated CD.

Acting via a novel mechanism, ALD1613, a neutralizing monoclonal antibody to ACTH, reduced plasma cortisol levels >50% in a recent study on non-human primates.

Although larger studies are needed, combining drugs, whether from the same or different classes, could potentially increase the number of patients in whom Cushing can be controlled, while also minimizing adverse effects.

In the long run, choice of medical therapy should be based on the individual clinical situation and benefit–risk ratio.

The author is a scientific consultant and principal investigator with research support to OHSU for Novartis, Chiasma, Cortendo and Pfizer.
Medical Treatment in Cushing Disease: Adrenal Focused

Richard Feelders

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Active Cushing syndrome (CS) is associated with multisystem morbidity and a decreased life expectancy mainly due to cardiovascular disease. Treatment should aim to completely normalize cortisol production to reduce morbidity and mortality. Medical treatment of CS can be indicated: (1) as pretreatment before surgery; (2) after surgical failure; (3) as bridging therapy after radiotherapy and (4) in patients who are no surgical candidates. Adrenal blocking drugs suppress cortisol production by inhibition of steroidogenic enzyme activity in the adrenal cortex. These steroid synthesis inhibitors include ketoconazole, metyrapone, mitotane and etomidate. Ketoconazole and metyrapone are most widely used and have a comparable efficacy with normalization of cortisol levels in 50-70 % of patients. Side effects of ketoconazole include gastrointestinal complaints and hepatotoxicity, whereas metyrapone treatment can worsen or cause hirsutism, hypertension and edema. Mitotane is mainly used for treatment of adrenal carcinoma. In critically ill patients with CS, in an intensive care setting, etomidate can rapidly decrease cortisol production. Generally, a combination of drugs is necessary in patients with severe hypercortisolism. Osilodrostat (LC1699) and levoketoconazole (COR-003) are recently developed steroid synthesis inhibitors. Osilodrostat is an inhibitor of 11-b-hydroxylase which catalyzes the last step in the synthesis of cortisol. A pilot study with osilodrostat in 12 patients showed promising results and efficacy and safety are currently investigated in a large multicenter phase III trial. Levoketoconazole is a 2S, 4R enantiomer of ketoconazole which inhibits cortisol production more potently and which is less hepatotoxic than racemic ketoconazole. Efficacy and safety of levoketoconazole are currently also examined in a large multicenter phase III trial.

Medical therapy for CS should be tailor-made taking into account patient characteristics, drug efficacy and potential side effects, severity of hypercortisolism and availability and costs.

The author receives research support from Novartis.

Predictors of Therapeutic Response in Acromegaly

Mónica Gadelha

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Surgery is considered the first choice therapy in the treatment of acromegaly in the vast majority of the cases. However, even in reference centers with skilled multidisciplinary teams, approximately half of the patients will require an adjuvant treatment.

To date, the recommendations for the treatment of acromegaly are based on a “trial and error” approach, with generalized recommendations for all patients and, therefore, first-generation somatostatin receptor ligands (SRL) are considered the mainstay of the adjuvant treatment. Nevertheless, approximately 70% of the patients are not fully controlled with first-generation SRL and, currently, other drugs are available. Therefore, the identification and validation of robust predictors of response to the different drugs will be fundamental for a more directed treatment. This will probably allow a faster disease control and a decrease in the economic burden to the health system since most of these drugs are expensive. Another important point that will be discussed during this talk is the aspects involved in the definition of resistance to first-generation SRL.

Some biomarkers have been proposed to be effective in predicting the response to first-generation SRL like high SSTR2 expression, high AIP expression, hypointensity in T2 at MRI, perinuclear expression of cytokeratins 7 and 8 (densely granulated adenoma), among others. Regarding, pasireotide LAR, a next-generation SRL, there is preliminary evidence that high SSTR5 expression may be a predictor of response. Potential predictors of response to cabergoline and pegvisomant will also be discussed.

In conclusion, with the evolving progress of translational medicine, the treatment of acromegaly in a near future will probably be based in an individualized approach and, therefore, we will be able to choose the right drug for the right patient at the right moment.

The author receives research support from Ipsen, Novartis, and Pfizer; honoraria from Ipsen and Novartis; and consulting fees from Ionis and Novartis.

This presentation will include discussion of product(s) unlabeled (off-label) for use as approved by the FDA or by the equivalent regulatory authority in the country in which the studies or trials were performed.
Should We Be Measuring GH, IGF-I or Both in Following Acromegaly Patients?

Peter Trainer

The Christie NHS Foundation Trust, Manchester, UK

Serum GH and IGF-I levels are closely correlated but discordance between GH and IGF-I levels occurs in approximately 25% of patients with acromegaly, either as a consequence of biological factors or as an artefact of the means of assessment or definitions of normality. The more common scenario is an elevated IGF-I and ‘normal’ GH with reverse being encountered less frequently. Whenever possible both GH & IGF-I data should be considered and reasons for discrepancy sought.

The exception is patients on GH receptor antagonist therapy which lowers circulating IGF-I and increases in GH, with IGF-I being the appropriate measure of disease activity. Another more subtle effect is that of oestrogen which induce a state of relative GH resistance, exemplified by the fall in IGF-I in pregnant patients. Studies with raloxifene have exploited this effect to lower IGF-I in men and women with acromegaly. Parkinson et al demonstrated that in women with untreated acromegaly serum IGF-I was 82 ng/ml lower than in men with equivalent GH levels, with the difference becoming 130 ng/ml in women on oral oestrogens. Mean IGF-I was 14 ng/ml lower in men with acromegaly on testosterone therapy, presumably a consequence of aromatisation. Increasing age was associated with a fall in IGF-I, for a given GH level.

Pituitary radiotherapy results in apparent discordance between GH & IGF-I levels as the former declines faster than the latter. Pulsatility studies indicate that circulating IGF-I values correlate most closely with trough GH values. 70% of circulating IGF-I is hepatic in origin so liver disease can result in impaired IGF-I generation.

A plethora of consensus statements and guidelines on the management of acromegaly have attempted to define the biochemical criteria of successful therapy. Vigilance is required when applying international criteria to local practice because of bias in assay performance and quality assurance concerns with some commercial kits. Re-examination of reference ranges has resulted in a significant lowering of the upper limit of reference ranges for IGF-I, such that a patient considered controlled by IGF-I criteria a decade ago may no longer be regarded as controlled.

When GH & IGF-I levels are grossly elevated the factors described above are of little clinical relevance. The true challenge of discordant results is in the patient with near ideal disease control in whom additional treatment is being considered. Unless the patient is on GH receptor antagonist therapy, decisions should be informed by both GH & IGF-I data taking into consideration the performance of the relevant assays and crucially patients’ symptoms.

Disclosures, if any, will be provided prior to the presentation.
Developing Criteria for Pituitary Tumor Centers of Excellence

Felipe F. Casanueva

Department of Medicine, Santiago de Compostela University, Complejo Hospitalario Universitario de Santiago (CHUS); CIBER de Fisiopatologia Obesidad y Nutricion (CIBERobn), Instituto Salud Carlos III; Santiago de Compostela, Spain

It is widely accepted that only experts in the field provide the best standard of care for patients and are able to significantly contribute to the advancement of Pituitary Science. Although everybody has an intuitive view of what a given team or group should have to be considered a Center of Excellence, an explicit and widely accepted definition of the characteristics and methods of such a center is lacking. The Pituitary Society as a leading organization should provide such definition.

To fulfill that task, an international group of experts in the topic was gathered to act as Steering Committee for developing criteria that were accepted by the Board of Directors of our Society. The different criteria including definition of expertise for endocrinologists, pituitary neurosurgeons and collaborating experts and units will be presented at this meeting and widely discussed.

The author receives consulting fees from Pfizer.

Developing Criteria for Pituitary Tumor Centers of Excellence: Neurosurgical Perspective

Pietro Mortini

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Pietro Mortini has no relevant relationships to disclose.
CRH/ACTH/CUSHING DISEASE

P1
A Case of ACTH Dependent Cushing Disease in Li-Fraumeni Syndrome
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Introduction: Li-Fraumeni Syndrome (LFS) is an autosomal dominant disorder with inactivating mutation of the tumor suppressor p53 gene. The syndrome is characterized by multiple malignancies, primarily sarcoma, breast cancer, leukemia and adrenocortical carcinoma. We present a case of Cushing disease (CD) in a patient with LFS. Association of pituitary adenomas with suppressor gene mutations has not been well established and corticotroph cell adenomas have not been reported in LFS. Case Report: 50 yo Hispanic female with a history of LFS, osteosarcoma of jaw (age-29), breast adenocarcinoma (age-36), hypertension, and type-2 diabetes, presented with worsening headaches. Brain MRI showed a heterogeneously enhancing 10x7x8mm pituitary adenoma. Repeat MRI in 18 months showed increase in the size of adenoma to 12x8x10mm. Patient’s symptoms included weight gain, heat intolerance, nausea, fatigue and worsening hyperglycemia. Physical examination was remarkable for acanthosis nigricans, rounded facies, and supraclavicular fullness. No use of exogenous glucocorticoids. Biochemical evaluation showed borderline high AM-cortisol 19.3mcg/dL(6.2-19.4mcg/dL), high ACTH 80pg/mL(6-58pg/mL), normal 24h urine free cortisol 23.9ug/g (<25ug/g), borderline suppression of am cortisol 1.77mcg/dL(<1.8mcg/dL) with 1mg dexamethasone, high midnight salivary cortisols x2: 0.069ug/dL and 0.105ug/dL(<0.090ug/dL). Her pituitary function was otherwise normal, including IGF-1, thyroid function, and prolactin. Given the clinical and biochemical findings, and interval increase in the adenoma size especially in the setting of a tumor suppressor gene mutation, patient underwent endoscopic trans-sphenoidal surgery. Pathology confirmed a corticotroph cell adenoma with diffuse ACTH immunostaining. Conclusion: We present a case of Cushing disease in a patient with Li-Fraumeni Syndrome. Pituitary adenomas or Cushing disease have not been previously reported in LFS. This case highlights the potential role of p53 gene mutation in the pathogenesis of corticotroph cell adenomas. Expression of p53 protein has been shown in pituitary adenomas but p53 gene mutations have not been associated with the development of pituitary tumors.

The authors have no relevant relationships to disclose.

P2
An EGFR Family Member, ERBB4 Expression Is Associated With Tumor Invasiveness In ACTH-Producing Pituitary Adenomas
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Background: EGF receptor (EGFR) is expressed in ACTH-producing pituitary adenomas (ACTHomas) and stimulates POMC expression and cell proliferation. Recently, a somatic mutation in USP8 gene has been identified as a cause of ACTHoma and the mutation resulted in the enhanced EGFR expression, indicating the importance of EGFR signaling in the pathogenesis. EGFR has 4 family members and we recently found that the expression level of ERBB4, which is one of the family members, was associated with the response of POMC expression to EGFR tyrosine kinase inhibitor, suggesting a pivotal role of ERBB4. ERBB4 has 2 functionally different splicing isoforms CYT-1 and CYT-2, and CYT-2 isoform reportedly suppress cell proliferation in medulloblastoma. In this study, we investigated the role of ERBB4 in the pathogenesis and characteristics of ACTHoma. Study design: Eleven of human ACTHomas were obtained and proceeded for RNA extraction. ERBB4 expression levels were measured by quantitative RT-PCR and the association with the clinical characteristics. The expression of CYT-1 and CYT-2 was analyzed using specific taqman probe. Results: Although ERBB4 expression level was not associated with plasma ACTH levels, serum cortisol levels and daily urinary free cortisol levels, that was significantly higher in the tumors with low-grade (0-1) of the Knosp classification than that in those with high-grade (2-3) (p = 0.01), suggesting that ERBB4 may negatively regulates the invasiveness. With regards to the isoforms, quantitative analysis demonstrated that the expression of CYT-2 was significantly higher than that of CYT-1 (p < 0.01), while normal pituitary predominantly expressed CYT-1. Discussion: These data suggest that predominant expression of CYT2 of ERBB4 may negatively regulate tumor invasiveness in ACTHoma. Further investigation is needed to clarify the pathophysiological role of ERBB4. Conclusion: ERBB4 CYT-2 isoform was predominantly expressed in ACTHomas and its expression level was associated with tumor invasiveness.

The authors have no relevant relationships to disclose.
P3
Bone Safety of Dual-Release Hydrocortisone (Plenadren®) in Patients with Hypopituitarism
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Chronic replacement with corticosteroids is mandatory in both primary and secondary adrenal insufficiency. The absence of reliable biochemical and/or clinical markers of adequate substitution may lead clinicians to overtreat these patients in order to avoid complications such as life-threatening adrenal crises. However, the deleterious effects of this overtreatment are well-known, including hyperglycemia and skeletal fragility. In glucocorticoid-induced osteoporosis the fracture risk precociously increases and is related to the dose and duration of glucocorticoid exposure. Plenadren®, the dual-release hydrocortisone formulation (DR-HCT) which better reproduces the endogenous cortisol rhythm, has recently become available but its safety on bone parameters is still unknown.

Aim of this prospective pilot study was to evaluate bone mineral density (BMD) as assessed by lumbar and femoral DXA (Hologic QDR4500W) before and after (15±3 months) switching the patients to DR-HCT.

We enrolled 11 patients (4M/7F, median age 57yrs, range 33-79yrs) with a long history of hypopituitarism in replacement therapies (2/11 with rhGH; 10/11 with levothyroxine). All patients had been chronically treated with hydrocortisone or cortisone acetate (median daily hydrocortisone or equivalent dose: 22.5mg) and then switched to the equivalent daily dose of DR-HCT.

No significant differences were found in biochemical and clinical parameters (glycemia, electrolytes, BMI, blood pressure) after the therapeutic shift towards DR-HCT and neither adrenal crises nor clinical fractures were reported during the observation period. A significant improvement in lumbar BMD (from -1.1SD, range -3.3 to +3.3 to -0.7SD, range -3.1 to +3.9SD; p=0.049) was observed during DR-HCT therapy. The T-score at femoral neck also tended to increase (p=0.08), whereas no significant changes occurred at the total hip (p=0.58).

These data support the bone safety of Plenadren® in hypopituitarism, possibly suggesting an advantage on BMD of this more physiologic substitution. Studies with a longer follow-up, higher number of patients and on hard clinical end-points are needed to confirm our preliminary findings.

The authors have no relevant relationships to disclose.

P4
Case Report: Pseudotumor Cerebri After Apoplexy in Cushing’s Disease
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Introduction: The development of pseudotumor cerebri is a rare complication after successful treatment of hypercortisolism. Its incidence is higher in children, affecting 3% of this population when submitted to surgical treatment of Cushing’s disease. We report a case where pseudotumor cerebri developed after an ACTH-secreting adenoma pituitary apoplexy. Case report: A 15-year-old girl was evaluated for progressive and rapid weight gain, hypertension and amenorrhea. On physical exam, there were conspicuous signs of Cushing syndrome: dorsocervical fat pad, purple striae, hyperpigmentation, acanthosis nigricans. While waiting further outpatient investigation, the patient developed severe headache, nausea, vomiting and dizziness. Brain MRI revealed in the intrasellar region a 8x6 mm hyperintense image in both T1 and T2 sequences suggestive of hemorrhage and pituitary apoplexy. The urinary free 24-hour cortisol collected after the episode was 7 mcg/24h (NR: 21 – 110 mcg/24h) and morning serum cortisol at 8 a.m. was 1.8 mcg/dl (NR: >3mcg/dl). Glucocorticoid replacement therapy with hydrocortisone was started and the patient was discharged asymptomatic. Two months later, she returned to the emergency department complaining of progressive blurred vision. Ophthalmoscopy revealed bilateral papilledema. There were no abnormalities in her level of consciousness nor on neurological examination. Brain MRI revealed only an hypothrophic adenohypophysis, but no expansile lesions, indicating pseudotumor cerebri as the cause of the patient’s current symptoms. Diuretic therapy was then initiated. Discussion: Cortisol plays an important role in maintaining CSF homeostasis. Any disturbance in the hypothalamus–pituitary–adrenal axis leading to an abrupt decrease in cortisol levels may result in pseudotumor cerebri. Conclusion: Pseudotumor cerebri is a rare complication of hypercortisolism treatment. To the best of our knowledge, this is the first case describing the development of pseudotumor cerebri after ACTH-secreting pituitary adenoma apoplexy. Its recognition and adequate treatment is paramount for the prevention of ophthalmologic sequelae.

The authors have no relevant relationships to disclose.
Central Serous Chorioretinopathy: A Complication in Cushing’s Disease

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Background: Cushing’s disease is associated to higher morbidity and mortality. The complications like arterial hypertension, diabetes and osteoporosis are frequently seen. Other rare complications may be present. The central serous chorioretinopathy (CSCR) is an entity that affects central retina. Although underlying pathological mechanisms are not fully understood, a correlation between chronic steroid use and CSCR was suspected. It affects mainly young males, it is usually unilateral and, although it can resolve spontaneously, sometimes, it could lead to long-term visual damage. Clinical case: We present a 36-year-old man who had a clinical typical Cushing syndrome. Biochemical investigations indicated ACTH-dependent Cushing syndrome. MRI showed a pituitary micro adenoma. The visual field showed scotomas in the right eye. He had mild visual alterations. A corticotroph adenoma with Ki 67: 1% was removed. The patient persisted with active CD after surgery. He was put on Ketoconazole treatment for three years with good clinical and biochemical response. Then, the treatment was stopped and the patient did not require medical treatment for two years until relapse of Cushing syndrome. At this moment, he referred visual symptoms: blurred vision and metamorphopsia in the right eye, and the ophthalmologist diagnosed CSCR. These lesions were confirmed by optical coherence tomography (OCT). There was no evidence of intraocular inflammation, retinal holes, tears, or retinal choroidal neovascularization. No specific treatment was prescribed for the CSCR, and 6 months later a total remission of CSCR was observed in association to the improvement of the CLU. Conclusions: Central serous chorioretinopathy (CSCR) develops in up to 5% of patients with Cushing syndrome, and our case underlines the relevance of high cortisol levels in its pathogenesis.

The authors have no relevant relationships to disclose.

Clinical Parameters to Distinguish Silent Corticotroph Adenomas from Other Nonfunctioning Pituitary Adenomas

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Silent corticotroph adenomas (SCAs) are clinically nonfunctioning pituitary adenomas (NFPA) with positive staining for ACTH by IHC. While preoperative features are similar to those of other NFPA, SCAs tend to have a more aggressive postoperative course compared with other NFPA. We evaluated the clinical parameters to distinguish SCAs from other NFPA.

We reviewed the medical records of 417 patients who underwent TSA for NFPA between 2011 and 2016 at the Severance Hospital Pituitary Tumor Clinic. We included patients who had undergone CPFT, 24hr UFC, IHC staining and who had not undergo prior TSA. A total of 341 patients were enrolled.

The patients were consisted of 37 SCAs and 304 other NFPA. Age and tumor size were similar between SCAs and other NFPA. The ratio of female (89.2 vs. 57.6%, P<0.001) was higher and Intratumoral hemorrhage (32.4 vs. 9.2%, P<0.001) in sella MRI was more frequent in SCAs than in other NFPA. In preoperative CPFT, cortisol response was not statistically different between SCAs and other NFPA. Peak ACTH (67.80±49.83 vs. 85.67±78.97pg/mL, P=0.061) was tend to have lower levels in SCAs than in other NFPA and ΔACTH (53.71±50.14 vs. 72.67±75.82pg/mL, P=0.046) was significantly lower in SCAs than in other NFPA. When we excluded hypopituitarism patients, peak ACTH (81.52±50.58 vs. 99.32±81.52pg/mL, P=0.042) and ΔACTH (64.88±49.26 vs. 86.94±77.79pg/mL, P=0.037) were significantly lower in SCAs than in other NFPA. It means that ACTH response in SCAs was decreased in response to hypoglycemia.

These data provide the evidence that female patients, Intratumoral hemorrhage in sella MRI and decreased ACTH response in CPFT should be noted that there is a possibility of SCAs.

The authors have no relevant relationships to disclose.
FIFTEENTH INTERNATIONAL PITUITARY CONGRESS

Hypercoagulability in Cushing Disease: A Risk Awareness and Prophylaxis Survey on Behalf of the Pituitary Society

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Introduction: Hypercoagulability leading to venous thromboembolism (VTE) has been increasingly recognized in Cushing syndrome patients and some centers administer prophylactic therapy. As a Pituitary Society pragmatic initiative, we surveyed centers from around the world experienced in the treatment of Cushing disease (CD) to assess current practices regarding managing VTE in CD, postoperative glucocorticoid (GC) use and preoperative routine use of antihypercortisolemic medications in CD. We report results of two written surveys conducted at consecutive Pituitary Society meetings in 2013 and 2015 to assess current practice and changes over time. Methods: Survey comprised 17 questions designed by one investigator and edited by 4 others. Results: The respondents represented 60 centers in 2013 (35% from US, 34% Europe, 10% South America, 10% Asia, 5% Australia, 6% unclassified) and 33 in 2015. Findings, including changes in practice over 2 years, are summarized in Table 1. Over 75% of respondents favored the need for further research in this topic. Discussion: This study is the first to provide information on international clinical practice regarding VTE in CD. Awareness regarding hypercoagulability in CD quadrupled in 2 years; routine VTE prophylaxis increased from 50% to 75% perioperatively and doubled in patients who underwent BIPSS. However, prophylactic treatment for hypercoagulability was not universally administered despite published data on such benefits. Postoperative GC use was stable over 2 years, while use of preoperative antihypercortisolemic doubled. Limitations include that only a subset of Pituitary Society members completed the survey and responses were based on recall. A major strength was inclusion of many international tertiary centers with expertise and a large volume of CD patients. Conclusions: Over a short period, awareness about risk of hypercoagulability has increased among clinicians treating CD. Large controlled trials to investigate the best treatments for VTE prevention in CD are needed to prevent hypercoagulability morbidity and mortality.

<table>
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<th>2013</th>
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<td>%</td>
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<td>Routine VTE prophylaxis during IPSS</td>
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<td>Low molecular weight heparin for a duration of 1-2 weeks</td>
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<td>Routine use of preoperative medical therapy in patients with CD</td>
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<td>Routine use of glucocorticoids after pituitary surgery in all patients with CD</td>
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P8

Improvement in Clinical Signs and Symptoms of Cushing Disease During 12 Months’ Therapy with Monthly Pasireotide

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Introduction: A once-monthly, long-acting formulation of pasireotide, a multireceptor somatostatin analogue, significantly reduced mean urinary free cortisol (mUFC) in patients with Cushing disease (CD) in a multicenter, randomized-dose, double-blind, Phase III trial (Newell-Price et al. Endocrine Abstracts 2016;41:GP153). The effects of long-acting pasireotide on signs and symptoms of CD are reported here. Methods: Patients with persistent/recurrent (n=123) or de novo (non-surgical candidates; n=27) CD and mUFC≥1.5–5xULN were randomized to monthly pasireotide 10mg (n=74) or 30mg (n=76). Dose could be up-titrated (10 to 30mg/30 to 40mg) at month (M) 4 if mUFC>1.5xULN and/or at M7, M9, or M12 if mUFC>1.0xULN. Primary endpoint was mUFC<ULN at M7, regardless of dose titration. Signs/symptoms of CD were evaluated at regular intervals. Results: Reductions in mUFC were accompanied by substantial clinical improvements. Mean changes (95%CI) in clinical signs from baseline to M12 in the 10mg and 30mg groups included: waist circumference, –4.5cm (–7.2, –1.8) and –6.2cm (–8.7, –3.6); BMI, –1.3kg/m2 (–1.8, –0.8) and –2.6kg/m2 (–3.3, –1.9); weight, –3.4kg (–4.8, –2.0) and –6.5kg (–8.3, –4.7); health-related QoL score, 6.4 (1.3, 11.6) and 7.0 (3.0, 10.9). Clinically relevant decreases in systolic (<5.0mmHg [–8.8, –1.3]) and diastolic (<3.1mmHg [–5.7, –0.5]) BP were reported in the 30mg group, with similar trends in the 10mg group. Statistically significant (P<0.0001) relationships were found between changes in mUFC and systolic/diastolic BP, after adjusting for antihypertensive medication. Clinical changes were observed irrespective of whether patients achieved mUFC<ULN at M7. The safety profile of long-acting pasireotide was similar to that of twice-daily pasireotide (Colao et al. N Engl J Med 2012;366:914–924). Conclusion: Long-acting pasireotide provided substantial improvements in signs and symptoms of CD over 12 months’ therapy. Long-acting pasireotide is an effective treatment option for patients with CD, with a convenient monthly administration schedule.

Pritam Gupta is a Novartis employee; Andre Lacroix receives consulting fees from Novartis and is an investigator for Strongbridge; Stephan Petersenn honours and consulting fees from Novartis; Rosario Pivonello receiving consulting fees and honoraria from Novartis; Jochen Schopohl does contracted research and is on the Board of Novartis and Ipsen and does contracted research for Pfizer and OPKO; Libuse Tauchmanova is a Novartis employee; the other authors have no relevant relationships to disclose.

P9

Pituitary Apoplexy of ACTH-secreting Pituitary Adenomas – Not Such a Rare Condition?

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Objective: Thunderclap headache and visual disturbances are clinical features of pituitary apoplexy (PA), the sudden infarction of and/or hemorrhage into a preexisting pituitary adenoma. Not all adenoma subtypes seem to be at equal risk for PA, which occurs most often in non-functioning pituitary macroadenomas. Adrenocorticotropic hormone (ACTH) secreting tumors leading to the clinical entity of Cushing disease (CD) are almost exclusively microadenomas and are most often diagnosed via the typical clinical features of the underlying endocrinopathy. In the literature, only isolated cases of PA in ACTH-secreting pituitary adenomas are reported, the largest series so far comprising 5 patients. Methods: Within the framework of a retrospective analysis, we reviewed the chart records of patients with proven PA (by means of MRI imaging and/or histology) referred to the neurosurgical department of our university with respect to the typical clinical features of CD, positive ACTH-immunostaining and/or recurrence of CD after PA in order to identify infarcted ACTH-secreting adenomas. Results: Of 68 patients with PA (31 male, 37 female), 6 presented prior to PA with the typical clinical features of CD. In 4 of these, central hypercortisolism had also been proven biochemically. 7 histologies revealed positive ACTH-immunostaining and in 2 patients clinical features of CD in addition to biochemical disease recurrence were seen 7–9 years after PA, necessitating medical or radiotherapy. Conclusion: The in proportion to the overall study group high number of patients with PA and underlying CD/ACTH-staining adenomas leads us to conclude that hemorrhage into this adenoma type is not such a rare entity as previously thought. A putative pathophysiological mechanism might pertain to hypercortisolism-induced fragility of the vasculature supplying such adenomas leading to infarction and/or hemorrhage. Further research into this matter is indicated.

The authors have no relevant relationships to disclose.
P10
Pregnancy-associated Cushing Disease
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Introduction: Cushing disease is known to disproportionately affect women of child-bearing age, and based on anecdotal evidence, may have an increased incidence during or immediately following pregnancy. Literature review reveals only a single published case report of pregnancy-associated Cushing disease and multiple case reports of pregnancy-associated, ACTH-independent Cushing syndrome caused by adrenal adenomas. Herein we sought to establish the incidence and characteristics of Cushing disease associated with pregnancy. Methods: A retrospective review of our prospectively gathered pituitary surgical database was conducted for patients with surgically proven Cushing disease. Patient demographics, clinical history, pathology and outcomes were reviewed. We defined “child-bearing age” as 15–45 years. Symptom onset of Cushing disease associated with pregnancy was defined as occurring up to one year after delivery. Results: From September 2007 to August 2016, 77 patients (65 women, 12 men) with Cushing disease were identified. Of the 65 women, 31 were of child-bearing age at the time of Cushing disease diagnosis. Eleven of these 31 (35.5%) women noted symptom onset associated with pregnancy (mean age 29.6 ± 4.14 years). Of these 11 patients, all had microadenomas (average diameter 7.90 ± 2.95mm). Pathology was typical adenoma in all cases (Ki67 ranging from 1% to 12%; all with low p53 staining). Additional demographics of this cohort and comparisons between women who developed Cushing disease not associated with pregnancy will be presented. Discussion: In a consecutive series of surgically confirmed Cushing disease, one third had onset of disease in the peripartum period. This relatively high rate of pregnancy-associated Cushing disease suggests a causal relationship possibly related to the stress of pregnancy and known hyperactivity of pituitary corticotrophs during pregnancy and the post-partum period. Further investigation of this relationship is warranted.

The authors have no relevant relationships to disclose.

P11
Surgical Outcome of Cushing Disease: A Single Center Experience In PUMCH
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Objective: To analyze results of transsphenoidal surgery in 341 consecutive patients. Methods: All the 341 patients accepted transsphenoidal surgery. Medical records were reviewed for patients treated with surgery for Cushing disease from 2011 to 2015. Radiographic features, pathology, remissions, recurrences, and complications were recorded. Results: Females comprised 81%(277/341) and male 19%(64/341) of patients. Imaging showed 66.7% microadenomas, 7.4% macroadenomas, and 22.8% negative for tumor. Remission rates for microadenomas, macroadenomas, and negative imaging were 83%, 66%, and 76%, respectively. Pathology showed adrenocorticotropic hormone-secreting adenomas in 83% of positive imaging, in 76% of negative imaging. Remission rates for pathology negative and positive were 57% and 87%, respectively. Remission rates for invasive microadenomas and macroadenomas were 19% and 50%, respectively. The recurrence rate was 16.7%. There were no operative deaths. Conclusion: Transsphenoidal surgery provides a safe and effective treatment for Cushing disease.

The authors have no relevant relationships to disclose.
P12
Synchronous Pituitary Adenomas Causing Cushing Disease and Acromegaly
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Context: This case of both Cushing Disease and acromegaly due to distinct synchronous pituitary adenomas is the first report of two or more simultaneous adenomas with distinct histological and immunohistochemical (IHC) features confirmed with RT-PCR. Case Description: A 68yo woman presented for neuroendocrine evaluation, which revealed 2 elevated late-night salivary cortisols (7.6 and 5.7 nmol/L (≥4.3)), 5 normal 24-hour urine free cortisols, normal serum prolactin (PRL), elevated insulin-like growth factor-1 (IGF-1) (302 ng/mL (75-263)) and borderline growth hormone (GH) suppression on oral glucose tolerance test (OGTT) (nadir GH 1.0 ng/mL). MRI demonstrated a 20 x 17 x 9 mm left sellar lesion. Transsphenoidal surgery revealed an adenoma with IHC staining showing most tumor cells reactive for ACTH, rare staining for PRL, and negative staining for GH, betaTSH, betaFSH, betaLH, and alpha subunit. Post-operative adrenal insufficiency confirmed remission from Cushing Disease, but serum IGF-1 level remained elevated (420 ng/mL (41-279)) with nadir GH 1.1 ng/mL on OGTT. Post-operative MRI showed a right sellar 6 x 5 x 3 mm lesion that appeared distinct from the left sellar lesion. A second transsphenoidal surgery revealed a second adenoma, with IHC staining demonstrating most tumor cells reactive for GH and betaFSH, many for PRL and alpha subunit, some for betaLH, rare for betaTSH and negative ACTH staining. Post-operatively, serum IGF-1 level (189 ng/mL (41-279)) was normal. RT-PCR of the first tumor detected ACTH RNA but not GH, PRL, betaTSH, or alpha subunit. There was insufficient tissue from the second tumor to perform RT-PCR. Discussion: Case reports of synchronous tumors have remained limited to IHC. This is the first report of synchronous functioning pituitary adenomas confirmed using differential RNA expression of ACTH and GH.

The authors have no relevant relationships to disclose.

P13
Temozolomide Therapy for Aggressive Pituitary Tumor Causing Cushing Disease
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Objective: The management of pituitary tumors causing Cushing Disease is a multidisciplinary challenge to clinicians with neurosurgery as a first line treatment followed by the radiotherapy and chemotherapy. Such tumors are difficult to treat with high rate of recurrence. Temozolomide (TMZ) is an alkylating chemotherapeutic agent that has recently been used in some cases as a new therapeutic tool for pituitary aggressive adenomas. To date only 25 patients with Cushing Disease treated with temozolamide have been reported. Materials and method: 61-year-old male patient was diagnosed as Cushing Disease in the course of macroadenoma in 2011. Patient underwent four transphenoidal non-radical neurosurgeries (2012,2013) with postsurgical insufficiency of gonadal and thyroid axis, repeated non-radical bilateral adrenalectomy (2012, 2013) and stereotactic radiotherapy and gamma knife surgery (2013, 2015). Histopathological examination revealed macroadenoma with high cell polymorphism and presence of the Crooke’s cells. Patient has been treated with 600 mg of ketokonazol. From 2015 treated with 6 cycles of temozolamide with important clinical improvement with the 23-25% decrease of morning and midnight cortisol and the decrease of ACTH from 1317 to 689 pg/ml. In the control MRI the size of the tumor was the same as in the previous MRI (30x35x35 mm). There were not side effects of TMZ. After oncological consultation the decision to continue TMZ treatment was undertaken. After the 9th cycle of TMZ in XII 2015 in the PET examination there was an increase in the size of the tumor to 35x53x54 mm. ACTH increased to 779 pg/ml, with morning and midnight cortisol increase. The sudden clinical status and sight deterioration and hearing loss were observed. Patient died on February 2015. Conclusions: The treatment with TMZ was effective and safe during first 6 cycles with progression observed during the continuation of the treatment. Further studies on the effectiveness of TMZ and other agents should be continued in patients with corticotrophin tumors resistant to conventional therapy.

The authors have no relevant relationships to disclose.
P14
Genetic Analysis in Japanese Kallmann Syndrome and Idiopathic Hypogonadotropic Hypogonadism
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We examined the genetic abnormalities in 11 cases of Japanese Kallmann syndrome (KS) and 8 cases of idiopathic hypogonadotropic hypogonadism without anosmia (IHH). These patients had accessed our KS support web site “http://kallmannsyndrome.jp/” and/or visited our endocrine department from areas all over Japan. Patients were diagnosed as having the isolated hypogonadotropic-hypogonadism due to the results of hypothalamic GnRH deficiency with or without anosmia. Gene abnormalities were examined by next generation sequencer (MiSeq) and abnormal sites were confirmed by Sanger methods. The 29 candidate genes, CHD7, FGF8, FGFR1, FSHB, GNRH1, GNRHR, GNRI, HESX1, HES6ST1, ANO1/KAL1, KISS1, KISS1R, LEP, LEPR, LHB, LHX3, LHX4, NELF, NROB1, OTX2, POU1F1, PROK2, PROK2R, PROP1, SEMA3A, SOX2, SOX3, TAC3, TACR3, WDR11, were analyzed in all patients (ethical approval was obtained). We found gene abnormalities in 4 of 11 cases in KS and 3 of 8 cases in IHH. Compared with the clinical findings in each group with or without gene abnormality, no specific difference was found. In this study, the gene abnormality ratio in KS cases was 36% and in IHH cases was 37%. In conclusion, KS and IHH are genetically heterogeneous and pathologically complex syndromes. In our study of over 60% patients with KS or IHH, no genetic abnormality was found. This result shows that, we must progress our study for searching other candidate genes or examine the cause of abnormalities other than genetic abnormalities.

The authors have no relevant relationships to disclose.

P15
The Expression of p110α and p85α were Associated with the Knosp Classification of Non-functionary Pituitary Adenomas
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Context: It has been reported that those non-functionary pituitary adenomas (NFPAs) that extend into the cavernous sinus were neither aggressive nor invasive. It is the weakness of the medial wall of the cavernous sinus that caused the invasion. And it has also been reported for several times that the PI3K-Akt-mTOR signaling pathway was over-activated in NFPAs. But the precise mechanism was not clear yet. Objective: To investigate the relationship between the PI3K-Akt-mTOR signaling pathway and the Knosp Classification of NFPAs and to make out the role of p110α and p85α to the over-activation of PI3K-Akt-mTOR signaling pathway in NFPAs. Design, setting and participants: We detected the expression of the main upper stream components (p110α, p85α, AKT, p-AKT and PTEN) of PI3K-Akt-mTOR signaling pathway in NFPAs from 16 knosp 0 grade NFPAs and 15 knosp 4 grade NFPAs and 5 normal pituitary glands from donation by qRT-PCR, immunohistochemistry (IHC) and western blotting. Results: In our study, we found that the p110α was over-expressed and AKT was over-activated in Knosp 4 grade NFPAs compared to Knosp 0 grade NFPAs (p < 0.05), while p85α and PTEN was under-expressed (p < 0.05). Conclusion: The expression of p110α and p85α were associated with the Knosp classification of NFPAs. And the over-activation of PI3K-Akt-mTOR signaling pathway in NFPAs may be related to the higher expression of p110α and the lower expression of p85α.

The authors have no relevant relationships to disclose.
P16
Acromegaly Status and Vitamin D Levels
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Introduction: Studies [1,2,3] have suggested that low serum levels of 25 hydroxyvitamin D (25OHD) are found in acromegaly, depending on the status of disease. Endocrinology, University of Medicine and Pharmacy ‘Gr.T.Popă’, Iasi, Romania. Objectives: The aims of this study were: 1. To evaluate serum calcium, phosphate, PTH and 25OHD serum levels in acromegalic patients. 2. To determine the association between 25OHD levels and disease activity. Methods: The study included 281 acromegalic patients (161 female), mean age 48.6±3.3 yrs. Normal age-matched IGF-1 values was the criteria for classifying patients as controlled and with active disease. 25OHD levels (ng/mL) were stratified into two categories: normal levels (≥30) and insufficiency (<30). IGF-1 values were expressed as times above upper limit of the normal range (xULNR). Data are presented as mean and standard deviation. The tests used to evaluate disease control / cure with continuous and categorical variables were t-student and chi-square, respectively. Results: In the whole series, mean level of 25OHD was 24.1±9.4 ng/mL and only 26% of patients (n=73) had normal 25OHD levels (table1). All patients had normal renal function. GH/IGF-I values did not correlate with 25OHD. However, disease activity was associated with lower 25OHD values (P=0.004, table).

Table

<table>
<thead>
<tr>
<th>Acromegaly status</th>
<th>Controlled (n=100)</th>
<th>Active (n=181)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH (ng/mL)</td>
<td>1.6±6.4</td>
<td>29.3±102.0</td>
<td>0.007</td>
</tr>
<tr>
<td>IGF-I (ng/mL)</td>
<td>171.1±77.1</td>
<td>755.6±377.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>xULNR-IGF-1</td>
<td>0.6±0.2</td>
<td>2.8±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.3±0.5</td>
<td>9.5±0.5</td>
<td>0.025</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>3.7±0.5</td>
<td>4.1±6a.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>58.7±24.8</td>
<td>51.4±26.0</td>
<td>0.022</td>
</tr>
<tr>
<td>25OHD (ng/mL)</td>
<td>25.8±10.5</td>
<td>23.1±8.7</td>
<td>0.022</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.8±0.2</td>
<td>0.7±0.2</td>
<td>0.016</td>
</tr>
<tr>
<td>VitD &lt;30 (ng/mL)</td>
<td>144 (79.6%)</td>
<td>64 (64%)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Conclusions: VitD sufficiency was found in only 26% of acromegalic patients. In line with the literature [1,2], disease activity was associated with lower vitamin D value.

The authors have no relevant relationships to disclose.

P17
Aryl Hydrocarbon Receptor Interacting Protein (AIP) Mutation Prevalence in Sporadic Acromegalic Patients with Poor Versus Good Response to Somatostatin Analogues: A Case-Control Study
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Aim: To determine aryl hydrocarbon receptor interacting protein (AIP) mutation prevalence and AIP- and somatostatin receptor (SSTR) 1-5 expressions in acromegalic patients with good vs. poor response to somatostatin analogues (SRLs). Methods: A total of 97 acromegalic patients (62 females/28 males; 70 poor- and 27 good responders to SRLs) without a familial history of pituitary disorder were included. Local ethical approval was obtained. The AIP gene analysis was performed using standardized PCR. The ex-vivo tumor specimens were evaluated in regard to AIP and SSTR1-5 expressions via immunohistochemical staining. Results: The mean age at diagnosis of the patients was 40.4±10.4 years. Patients with poor response to SRLs were younger, exhibited higher pre- and postoperative tumor size, higher Ki-67 labeling index, lower postoperative 3rd month IGF-1 levels, higher preoperative tumor size, higher Ki-67 labeling index, lower postoperative 3rd month IGF-1 levels, and late remission rate than those with good response (p<0.05 for all). Several genetic variations of the AIP gene were detected. g.6462C>T, rs2276020 intronic variants were identified in 36 (34 with poor and 2 with good response) and 5 (4 with poor and 1 with good response) of the patients, respectively. A novel intronic heterozygous variant g.6944G>A was found in one patient with good response. These were predicted as polymorphism in prediction tools. A novel heterozygous synonymous mutation (R323R) was identified in one patient. Patients with poor response showed lower AIP and SSRT2A expression (p<0.05 for all), but similar SSTR2B, SSTR3, SSTR4, SSTR5 expressions as compared to those with good response (p>0.05 for all). AIP expression was positively and significantly correlated with SSTR2A, SSTR3, and SSTR4 expressions, respectively (p<0.05 for all). Conclusion: Although there was a low prevalence of AIP mutation in apparently sporadic acromegalic patients with both poor and good response to SRLs, there was a higher incidence of several genetic variations of undetermined significance in patients with poor response.

The authors have no relevant relationships to disclose.
P18
Cancer Prevalence in 562 Patients with Acromegaly at Diagnosis and Last Follow Up and in Comparison to a Nonfunctioning Pituitary Tumor Cohort

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In acromegaly, chronic GH and IGF-1 excess produce the diseases' characteristic clinical manifestations and multi-system comorbidities. It has been proposed that this long-term GH/IGF-1 exposure could increase these patients' cancer risk, but results of studies assessing this risk have been inconsistent. Therefore, we sought to examine cancer prevalence in our acromegaly cohort at diagnosis and after long-term follow up. We studied 562 acromegaly patients at diagnosis, 284 men (median age 43.9 yr., range 16.3-79.4 yr.) and 278 women (47.9 yr., 18.9 -85.8 yr.). Most patients (n=519) were from two consecutive surgical series spanning 1981 to 2015 (KDP, n=411) and 1992 to 2015 (JNB, n=108). At diagnosis, 58 patients (10.3 %) had at least 1 prior cancer and 5 of them had 2 cancers. Of the 63 cancers present at diagnosis, the most common were breast (32%), thyroid (14.3%), prostate (12.7%) and melanoma (9.5%). We prospectively followed 359 patients from the cohort for 6.7 yr. (median)(range 0.5-33 yr.) from diagnosis to after surgery and adjunctive therapy. In these 359 patients, 40 new cancers developed and at last follow up, 61 patients (17%) had had 1 or more cancer (67 cancers total). Cancer prevalence was compared to that at diagnosis in a prospectively followed cohort of 275 clinically nonfunctioning pituitary adenomas (CNFPA) (49% men, 51% females) from the same referral population. Acromegaly males at last follow up were younger than CNFPA males, 52 yr. (18.8-89.6) vs. 59 yr. (26-86)(p<0.001), but females were similar in age, 55 yr. (20.5-99.4) vs. 55 yr. (24-81)(p=0.69). Cancer prevalence was greater at last follow up in the prospective acromegaly cohort (18.6%) compared to cancer prevalence in the CNFPA cohort (10%)(p=0.004). In conclusion, long term follow up of treated patients may be needed to appreciate the full extent of lifetime cancer risk in patients with acromegaly.

The authors have no relevant relationships to disclose.

P19
Cardiac Function Changes in Acromegaly Patients

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Introduction: It is known that hypertension is a common complication seen in acromegaly patients due to the antinatriuretic effect of growth hormones (GH). Left ventricular hypertrophy and valvular heart disease are also common complications. In this study, we investigated the effect of GH normalization by surgery on cardiac functions of the acromegaly patients. Patients and methods: 41 acromegaly patients who experienced remission following their first surgery were subjected. The patients consisted of 13 males and 28 females, with a median age of 56 years (20-75 years). Endocrine and cardiac functions of these patients were investigated before surgery and 3 months after surgery. Result: Preoperative hypertension was detected in 49% of patients. In a multiple regression analysis with ejection fraction (EF), left ventricular mass index (LVMi), E/A wave ratio, severity of mitral valve stenosis as objective variables and age, preoperative GH value, IGF-1 standard deviation, blood pressure, and disease duration as explanatory variables, disease duration and EF were positively correlated, whereas E/A and age showed a negative correlation. Blood pressure was significantly lower following surgery (systolic blood pressure: 126mmHg → 124mmHg, P < 0.01). LVMi showed slight improvement (101.8 g/m2 → 97.7 g/m2, P = 0.01), but EF did not change (69.9% → 71.1%, P = 0.75). No significant changes in E/A before and after surgery were observed (0.90 → 0.91, P = 0.73). Discussion: Marked left ventricular hypertrophy is seen in acromegaly patients, which was slightly improved by postoperative GH normalization. Hypertension is one of the contributors to left ventricular hypertrophy, but there was no association between hypertension and LVMi in this study. The contributors to left ventricular hypertrophy and valvular heart disease among acromegaly patients most likely include factors other than hypertension, such as hyperkinetic cardiac function.

The authors have no relevant relationships to disclose.
**P20**

**Cardiovascular Involvement in Acromegaly Patients Scanned by 3.0T Quantitative Cardiac Magnetic Resonance and Correlations Analysis**

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*These authors contributed equally to this work

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**Objective:** Cardiovascular involvement is the leading cause of death in acromegaly patients. Cardiac magnetic resonance (CMR) have hardly been used in early diagnosis and quantification of heart involvements in Neurosurgery Department. The aim was to explore cardiovascular involvements and correlations with clinical data in acromegaly patients.

**Methods:** This study was approved by the Ethical Committee of Peking Union Medical College Hospital. Informed consents were obtained from patients before enrollment. Newly diagnosed, untreated acromegaly patients were consecutively enrolled. Growth hormone (GH) burden was defined as the product of GH and disease duration (month). All patients went through CMR with a 3.0T MR scanner at the basal, middle and apical left ventricular (LV) levels. T1 mapping and extracellular volume (ECV) measurements were based on AHA 16-segments model. Correlations between variates were compared with Pearson analysis. Native T1 and ECV among slices were compared by ANOVA analysis.

**Results:** Seventeen patients were enrolled. Myocardial contractility at basal slice had a positive correlation with GH burden ($r=0.531, p=0.028$). Insulin-like growth factor 1 (IGF-1) was negatively correlated with T1 of basal slice ($r=-0.671, p=0.003$), ECV of basal slice ($r=-0.622, p=0.013$) and ECV of apex slice ($r=-0.664, p=0.007$). Average per-slice Native T1 and ECV showed no significant differences among basal, middle and apical LV levels.

**Conclusions:** According to the findings of CMR, GH burden and IGF-1 can impact on the heart involvements in acromegaly. LV contractility had a positive correlation with GH burden. Both T1 and ECV at different slices correlate differently with IGF-1 level.

The authors have no relevant relationships to disclose.

**P21**

**Correlation Between T2 Weighted MRI Signal Intensity and Preoperative Metabolic Impairments in Patients with GH Secreting Pituitary Adenoma**

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**Objective:** T2 weighted MRI signal intensity of pituitary adenoma has been reported to correlate with responsiveness to medical treatment in acromegalic patients, which are partly associated with the different granulation patterns of GH secreting adenoma. This study assessed independent associations of quantitative T2 weighted MRI signal intensity with metabolic impairments among acromegalic patients.

**Methods:** A total of 120 newly diagnosed acromegaly patients were included. All patients were classified as hypo-, iso-, or hyper-intense group by quantitative analysis of T2 signal intensity in MRI. The metabolic parameters including body weight, body mass index, and both the pre- and post-glucose loaded glucose, insulin, free fatty acids, and GH during 75 gram oral glucose tolerance test (OGTT) were evaluated before and at 6 months after transsphenoidal adenomectomy (TSA). HOMA-IR scores were also evaluated.

**Results:** The results showed that 71 (60%) adenomas were hypo-intense, 25 (21%) iso-intense, 24 (20%) hyper-intense. T2-hypointense adenomas were significantly associated with higher OGTT GH level ($29.1 \pm 18 \text{ng/mL}$ vs. $10.4 \pm 4.5 \text{ng/mL}; P=0.004$), higher OGTT insulin level ($14.8 \pm 5.5 \mu\text{U/mL}$ vs. $9.93 \pm 1.5 \mu\text{U/mL}; P=0.014$), higher OGTT free fatty acid level ($415.0 \pm 151.0 \mu\text{Eq/L}$ vs. $563.0 \pm 95.4 \mu\text{Eq/L}; P=0.015$), and higher HOMA-IR score ($3.97 \pm 1.15$ vs. $2.46 \pm 0.6; P=0.024$), compared to hyper-intense adenomas. However, the patients with T2-hypointense adenomas experienced significantly more decrement of HOMA-IR at 6 months after TSA, which were comparable with other intensity groups.

**Conclusion:** The quantitative measurement of T2 weighted intensity of GH-secreting adenomas at diagnosis correlated with metabolic parameters in acromegaly patients.

The authors have no relevant relationships to disclose.
P22

Differential Expression of MicroRNAs in Development of GH-secreting Pituitary Adenoma

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Background: Recent studies suggest that aberrant microRNA (miRNA) expression profiles have been associated with tumor formation, migration, and invasion. However, the role of miRNA in development of pituitary adenoma is limited. Herein, we analyzed the differential expression of miRNA during the cascade of pituitary tumorigenesis, using of somatotroph-specific aryl hydrocarbon receptor interacting protein (AIP) knock-out (sAIPKO) mouse model. Objective: In this study we established the miRNAs involving GH secreting pituitary tumorigenesis by comparing the miRNAs of pituitary gland in control and tumorous condition in mice models.

Methods: To explore possible oncogenic factors in sAIPKO, we used a miRNA microarray to profile changes in the expression of miRNAs. RNA samples extracted from 3 groups (control, hyperplasia, and tumor) were analyzed by miRNA microarray. Candidate miRNAs were further validated in in vitro conditions. Results: 35 miRNAs were significantly changed during GH secreting pituitary tumorigenesis in sAIPKO mice. Analysis of qRT-PCR using sAIPKO model during the mouse pituitary adenoma progression and their contemporary littermate animals resulted in down regulation of miRNAs showing downward trend and upregulation of miRNAs showing upward trend in the progression of pituitary adenoma. In experiment of transient knock down of AIP in GH3 cells, 8 miRNAs (miR-216a-5p, miR-185-5p, miR-339-3p, miR-181d-5p, miR-342-3p, miR-652-3p, miR-485-3p, and miR-183-3p) were expressed similarly to sAIPKO model. Direct target genes of candidate miRNAs were also dysregulated in sAIPKO mouse model. Finally, differential expression of miR-652-3p, miR-216a-5p, and miR-339-5p in human GH-secreting pituitary adenoma were observed. Conclusion: miRNAs were differentially expressed between control and sAIPKO model. It suggests that miRNAs might be involved in the tumorigenesis of AIP-related pituitary adenoma.

The authors have no relevant relationships to disclose.

P23

Effects of Growth Hormone (GH) Receptor Antagonism and Somatostatin Analog (SSA) Administration on Quality of Life in Acromegaly

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Background: Acromegaly is associated with impaired quality of life (QoL) and hyperglycemia. The aim of this study was to investigate the effects of biochemical control of acromegaly by GH receptor antagonism vs. SSA therapy on QoL. Methods: After IRB approval, the Acromegaly QoL Questionnaire (AcroQoL), Rand 36-Item Short Form Survey (SF-36), Gastrointestinal QoL Index (GIQLI), measures of glucose homeostasis and IGF-1 levels (LC/MS, Quest Diagnostics) were obtained. Results: 124 subjects were studied; n=60 receiving SSA; n=31 receiving pegvisomant (PEG); n=33 active acromegaly (ACTIVE). There were no group differences in mean±SD age (SSA 53±13y; PEG 51±16y and ACTIVE 50±15y, p=0.89), BMI (30±7, 31±6 and 29±5kg/m2, p=0.79), sex (38% male, p=0.37) and race (89% Caucasian, p=0.89). Mean IGF-1 levels and Z-scores were higher in ACTIVE (665±230ng/mL; 3.8±1.1) vs. SSA and PEG groups, which did not differ from one another (174±51ng/mL; 0.5±0.7 and 164±48ng/mL; 0.4±0.7, respectively, p=0.0001 vs. active). The ACTIVE group had poorer QoL in the Appearance domain of the AcroQoL (38±26 vs. SSA and PEG 51±25 and 49±19, respectively, p=0.003). There were no differences in QoL between SSA and PEG. In an analysis excluding subjects with diabetes mellitus, fasting insulin, but not glucose, was lower in SSA and PEG compared to ACTIVE (fasting insulin 3.7±2.5 vs. 6.6±3.5 and 10.6±6.1IU/mL, p=0.0005). Higher IGF-1 Z-scores (all subjects) and glucose levels (patients without diabetes) were associated with poorer QoL in a number of QoL domains. Conclusion: Our data confirm the association of higher IGF-1 levels with impaired QoL in patients with acromegaly but do not suggest that QoL differs significantly between patients with normal IGF-1 levels receiving SSAs compared to those receiving Pegvisomant chronically. Moreover, our data suggest that higher glucose levels are associated with a poorer QoL in patients without diabetes.

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Funding Sources: This study was funded through an investigator-initiated (PI: Miller) grant from Pfizer.
Efficacy of Dopamine Agonists Compared with Somatostatin Analogues in Acromegaly
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Purpose: Although somatostatin analogues (SSAs) are recommended as the first-line medical therapy for acromegaly, dopamine agonists (DAs) are also a therapeutic option for treatment. We aimed to assess and compare the efficacies of DAs and SSAs in treating acromegaly in clinical practice.

Methods: We included 89 patients with acromegaly who took DAs (bromocriptine [BCT], n=63; cabergoline [CAB], n=11) or SSAs (n=15) as a primary medical therapy for more than 3 months in the Seoul National University Hospital.

Results: The CAB (45.5%) and SSA (33.3%) groups achieved random GH levels of < 2.5 ng/mL and the normal IGF-1 levels were significantly higher than in the BCT group (11.1%) (p=0.009). We further included all the patients with acromegaly (n=132) who had taken CAB, BCT, and SSAs as first- or second-line medical therapy. The CAB group showed similar efficacy as the SSA group in terms of the GH and insulin-like growth factor-1 (IGF-1) levels (57.6% for random GH level < 2.5 ng/mL, 42.4% for normal IGF-1 levels, 36.4% for both). Logistic regression analysis revealed that medications, age, GH level, or IGF-1 level before medication, hyperprolactinemia, and prior gamma-knife surgery or radiation therapy, did not affect the therapeutic response. High pretreatment GH levels predicted poor treatment outcomes (odds ratio [95% confidence interval]=0.95 [0.90-0.99]).

Conclusions: The efficacy of CAB in treating acromegaly with a relatively low cost was non-inferior to that of the SSAs. CAB may be considered as a first-line medical therapy in patients with acromegaly, i.e. patients with low pretreatment GH levels.

The authors have no relevant relationships to disclose.

Healthcare Disparities in the Diagnosis and Treatment of Acromegaly in the United States of America
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Objective: Our objective was to evaluate the clinical presentation and outcomes of acromegaly patients treated in a county hospital setting and a private Pituitary Center. Methods: Data were collected via retrospective chart review of 36 patients from the Harris Health System (Harris County) and 28 patients from the Baylor St. Luke’s Pituitary Center (PC), a tertiary referral center. Patients were cared for by the same endocrinologist (S.L.S.). Statistical comparisons between the 2 groups were made using chi-square analysis for the categorical variables and student’s t test for the continuous variables. Two-tailed Fischer Exact Test performed for all categorical variables.

Results: At baseline, patients from HHS presented with larger tumors, a higher prevalence of optic chiasm involvement and higher growth hormone (GH) and Insulin like growth factor-1 levels (IGF-1). There also was a higher prevalence of diabetes (p 0.0039), hypopituitarism (p 0.02), hypogonadism (p 0.0019), and acromegaly physical features (p 0.005) in the HHS population. The composition of the ethnic background of patients was significantly different for HHS and PC with regard to Hispanic (73 vs. 11%), African American (9 vs. 3%), Asian (9 vs. 7%), and non-Hispanic whites (9 vs. 73%). Only 10% of patients seen in HHS had some form of insurance. PC patients were predominantly US citizens (100 vs. 16.6%), with private insurance (100 vs. 2.7%). In spite of socioeconomic differences, the outcomes were comparable with similar GH and IGF-1 levels in follow-up. Notably, 63% HHS patients received medical therapy through patient assistance programs (PAP).

Conclusion: Significant disparities exist in the severity of disease at presentation for acromegaly patients seen in a county system compared to a private PC. However, near equivalent biochemical control is achieved. The significant influence in narrowing the health disparities gap was access to PAPs.

The authors have no relevant relationships to disclose.
P26
Higher Recurrence Rates in Silent Somatotroph Adenomas Compared to Silent Gonadotroph Adenomas – Large Single Center Experience
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**Background:** Nonfunctioning pituitary adenomas are common pituitary tumors, and usually harbor an indolent course. However, their clinical course is variable; reports suggest that silent corticotroph adenomas (SCA) are more aggressive and can become hormonally active. Data on clinical behavior of silent somatotroph, GH-staining adenomas (SGHA) is scarce. **Objectives:** Study characteristics of SGHA and compare them to those of SCA and silent gonadotroph adenomas (SGA) in our cohort of surgically-treated pituitary adenomas. **Methods:** Retrospective, IRB-approved analysis of SGHA surgically resected at OHSU (2006 -2016). SGHA definition: no clinical or biochemical evidence of acromegaly and positive GH-immunostaining. All patients were evaluated by a neuroendocrinologist using a uniform protocol. SGHA were compared to SCA and SGA operated at our center during the same time interval. Statistics: PASW 18; p < 0.05. **Results:** Of 814 surgeries for pituitary adenomas, 18 (2.2%) SGHA, 35 (4.2%) SCA and 70 (8.6%) SGA were identified. Mean age at diagnosis for SGHA was 44 yo, with a female predominance (78%). Imaging: mean tumor size was 1.7±1.1cm, 19% were invasive in cavernous/sphenoid sinus, compared to SCA: 2.4±1.1cm, 43% invasive; SGA: 2.9±2.0cm, 40% invasive (size: p=0.02, invasion: p=NS). During mean follow-up of 3.8 years (0.1-10.5), 2 patients developed elevated IGF-1 (11%), 6 patients (33%) needed a second surgery, 5 for tumor recurrence and 2 patients had a third surgery. Rate of surgical reintervention in SGHA was similar to SCA (29%), but higher than SGA (11%) (p=0.03). **Discussion:** In our cohort, SGHA presented with smaller tumors and appeared less invasive radiologically, but tended to have more recurrences, similar to SCA, compared to SGA. A third of SGHA recurred in follow-up and a small proportion progressed to a GH-secreting tumor. **Conclusion:** Silent somatotroph adenomas should be followed closely due to their higher likelihood of recurrence and potential of progression to clinical acromegaly.

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P27
Low Dose of Imatinib Mesylate Causes GH Reduction In Cultured Somatotropinoma Cells
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**Introduction:** Acromegaly is a neuroendocrine disorder caused by excessive secretion of growth hormone (GH). Current treatment includes surgery, radiotherapy and drugs like somatostatin or dopamine receptor agonist. In spite of combination of therapies cure rate is dismal. There is a quest for new therapeutic targets with optimal efficacy, least side effect with low cost in resource constraint countries. Tyrosine kinase inhibitor (Imatinib) has been shown to cause growth failure in pediatric chronic myeloid leukemia (CML) cases by targeting the GH/IGF-1 axis. There is no study to report the effect of TKI on somatotropinoma either in vitro or in vivo. Here we present data on the effect of Imatinib on GH release from primary cultures of human somatotropinomas and GH3 cell line. **Material and Method:** Differential expression of imatinib target (c-kit, VEGF, PDGFR-α and β) was studied on 157 pituitary adenoma samples. The results were confirmed using western blot and RT-PCR. Both GH3 cell line and primary culture of somatotropinomas (n=20) were cultured and treated with graded concentration of imatinib mesylate. The drug effects were studied using GH assay, cell viability assay, immunocytochemistry, electron microscopy and apoptosis analysis. The mechanism of action of imatinib was studied using human proteome profiling kit and bioinformatically by Consensus PathDB and String DB. **Results:** Somatotropinomas showed significantly higher cytoplasmic positivity for c-kit, PDGFR-β and VEGF to NFPA (P<0.009, P<0.001 and P=0.003, respectively). A low concentration (0.5µM) of imatinib showed maximum inhibition of GH secretion and increasing the dose did not impart any advantage to the inhibition. Imatinib inhibits GH secretion in both primary culture (P<0.01) and GH3 cell line (P<0.001). However, imatinib treatment does not affect cell viability (P>0.88) and apoptosis (P>0.06). The receptor tyrosine kinase array and bioinformatics analysis showed there is a crosstalk between GHR and PDGFR-β. Imatinib inhibits GH signaling via PDGFR-β/ PKC pathway. **Conclusion:** Imatinib inhibits GH secretion in somatotropinoma cells without affecting cell viability. This may open a new vista for management of somatotropinomas.

The authors have no relevant relationships to disclose.
P28
Motor Disability in Acromegaly: A Questionnaire-Based Estimation

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Introduction: Arthropathy is a common complication in acromegaly but there is not a consistent relation between x-ray findings and subjective discomfort. Thus establishing the degree of articular dysfunction in these patients is difficult. Aim: To estimate, in a large series of acromegalic patients, the degree of motor disability, its impact on the quality of life (QoL) and work productivity, and its correlations with disease-specific determinants. Study: 181 acromegalic patients (85 men, age 25–89 years) were enrolled in this cross-sectional study; 110 had normal IGF-I levels, 71 presented with high IGF-I levels. Duration of the disease varied from a few months to 49 years. Adenoma volume, GH/IGF-I levels, therapies and BMI were also registered. Eight validated questionnaires were administered: AcroQoL, Patient-assessed Acromegaly Symptom Questionnaire (PASQ), Visual Analogue Scale (VAS) for pain, Arthritis Impact Measurement Scale (AIMS), Work Productivity and Activity Impairment, General Health (WPAI:GH) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Correlations between questionnaire-derived scores of disability and QoL and the abovementioned disease-related parameters were calculated. Results: Results among the different questionnaires displayed high concordance and positive correlations: WOMAC pain vs VAS r = 0.63, p < 0.0001; sum of WOMAC pain and stiffness scores vs AIMS symptoms scores r = 0.84, p < 0.0001. The abovementioned scores correlated with QoL (r < 0.0001), work productivity scores (r < 0.04), BMI (r < 0.0021) and disease duration (r < 0.01), and were found in subject with high or normal IGF-I levels. Comment: This study has demonstrated in patients with acromegaly: a) a high degree of articular disability, which correlates with disease duration in both biochemically controlled and uncontrolled patients; b) a significant impact of motor impairment on QoL and work productivity; c) the possibility to quantify the degree of articular impairment by validated questionnaires. Estimation of joint impairment may be relevant for insurance purposes.

The authors have no relevant relationships to disclose.

P29
Normal Quality of Life (QoL) in Non-radiated Panhypopituitary Patients on No Growth Hormone (GH) Replacement Treated with Contemporary Glucocorticoid Doses

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Objectives: AGHD (adult growth hormone deficiency) was shown to be associated with lower QoL vs controls. However, effects of age, supraphysiologic doses of hydrocortisone, radiation therapy and sinonasal sequelae of surgery were never taken into account. We compared hypopituitary patients with AGHD after surgery alone (N=34) and surgery + XRT (N=17) with controls (N=43) who had sinonasal surgery for benign disease, recruited from pituitary and otolaryngology clinics, respectively. Growth hormone deficiency was defined as presence of at least 3 additional hormone deficiencies with low IGF-1 and/or GH <1.0 ng/ml during insulin tolerance test. Replacement with hydrocortisone, testosterone (in men), DDAVP and thyroxine was given. No estrogen was given in women. Mean hydrocortisone dose was 14.2 +/- 0.9 mg/day. No patient had ever been treated with GH. Methods: We administered disease-specific, QoL-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) and benign sinus disease specific, Sino-Nasal Outcome Test (SNOT-22) questionnaires in each group. Higher scores suggest poor QoL on both surveys. Data was analyzed by Student’s t-test and expressed as mean +/- SEM. P < 0.05 was considered significant. Study was approved by institutional review board. Results: Controls were slightly younger than hypopituitary patients (57.3 +/- 1.3 vs 61.6 +/- 1.8 years, p=0.03). Plasma IGF-1 in patients who had sinusonal surgery for benign disease, recruited from pituitary and otolaryngology clinics, respectively. Growth hormone deficiency was defined as presence of at least 3 additional hormone deficiencies with low IGF-1 and/or GH <1.0 ng/ml during insulin tolerance test. Replacement with hydrocortisone, testosterone (in men), DDAVP and thyroxine was given. No estrogen was given in women. Mean hydrocortisone dose was 14.2 +/- 0.9 mg/day. No patient had ever been treated with GH. Methods: We administered disease-specific, QoL-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) and benign sinus disease specific, Sino-Nasal Outcome Test (SNOT-22) questionnaires in each group. Higher scores suggest poor QoL on both surveys. Data was analyzed by Student’s t-test and expressed as mean +/- SEM. P < 0.05 was considered significant. Study was approved by institutional review board. Results: Controls were slightly younger than hypopituitary patients (57.3 +/- 1.3 vs 61.6 +/- 1.8 years, p=0.03). Plasma IGF-1 in patients who had sinusonal surgery for benign disease was pathologically low at 83 +/- 7 ng/ml. In the entire group, AGHDA score was worse than in controls (7.7 +/- 0.9 vs. 5.2 +/- 1, p=0.04). However, this difference disappeared when controls and non-radiated patients were compared (5.2 +/- 1.0 vs 6.6 +/- 1.2, p=0.4), and entire difference was driven by radiated group (9.9 +/- 1.6, p=0.01). SNOT-22 scores did not differ between controls and patients as a whole (16.4 +/- 2.1 vs. 21 +/- 2.4, p=0.15). Conclusion: We conclude that when compared with controls of their own age group, patients with AGHD treated with contemporary doses of glucocorticoids but having no history of cranial radiation have normal quality of life despite absent GH replacement.

The authors have no relevant relationships to disclose.
**P30**

**Postoperative Lipid Metabolic Change of Acromegaly**

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**Introduction:** Acromegaly is caused by hypersecretion of growth hormone (GH). Hypersecretion of GH induces hypertension, overt diabetes and hyperlipidemia at a high rate. It is said that when the GH levels are normalized with proper treatment, most of these complications improve. In this study, we evaluated the significance of the different nadir GH cut-offs in OGTT (patients who meet the Cortina consensus criteria versus patients who meet strict new standards) and observed lipid metabolism changes following transsphenoidal surgery. **Patients and Methods:** 40 acromegaly patients who experienced remission following their first surgery were subjected. The patients consisted of 16 males and 24 females. We divided the patients into two groups according to nadir GH cut-offs in OGTT at 3 months after surgery (new criteria group: nadir GH below 0.4ng/mL; Cortina criteria group: nadir GH between 0.4 and 1.0ng/mL), and evaluated lipid metabolic changes (total cholesterol, T-C; LDL-cholesterol, LDL-C; and triglyceride, TG) between the two groups one year after surgery. **Results:** In the new criteria group (n=25), pre surgery T-C:LDL-C:TG(mg/dl) was 185.3:106.2:113.0, and one year following surgery was 190.0:113.0:88.7. In the Cortina criteria group (n=15), pre surgery T-C:LDL-C:TG was 181.5:104.6:96.0, and one year following surgery was 182.9:104.6:64.0. TG levels were decreased one year following surgery in both groups (P - value=0.04 and 0.01), but there were no significant changes in T-C and LDL-C levels. There were no significant differences between the two groups in lipid metabolism. **Discussion:** In this study, there was no noticeable improvement in the first year following surgery, except for TG. Also, between the two groups, there were no significant differences in the lipid metabolism. Future prospective studies with long-term follow-ups are required to determine if improvements in lipid metabolism are observed by meeting the strict new criteria.

*The authors have no relevant relationships to disclose.*

**P31**

**Pre- and Postoperative Characteristics of Body Composition and Metabolism in Acromegaly Patients: A Prospective Study**

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**Objective:** To examine the characteristics of body composition and metabolism in acromegaly patients and the effect of transsphenoidal surgery. **Methods:** Newly diagnosed, untreated acromegaly patients were consecutively enrolled, and age-, sex-, height-, weight- and race-matched patients with pituitary non-functional adenomas were selected into the control group. We measured sclerotin, protein, muscle, water content, visceral fat index, protein, total, intracellular and extracellular fluid, total energy expenditure and basal metabolism by Metabolic Analysis Apparatus in both group preoperatively. Same indexes were measured in acromegaly group 3 months after surgery. Comparisons of qualitative and quantitative variables were analyzed using χ2 test and t-test respectively. This study was approved by the Ethical Committee of Peking Union Medical College Hospital. Informed consents were obtained from patients before enrollment. **Results:** We prospectively enrolled 54 patients (36 acromegaly patients and 18 controls). The sclerotin, skeletal muscle mass, visceral fat index, protein, total, intracellular and extracellular fluid, total energy expenditure and basal metabolic rate were significantly elevated and the triceps skinfold thickness was all significantly decreased in patients with acromegaly (p<0.05). However, this trend was only found in male and patients under 40. In the postoperative period, the triceps skinfold thickness increased and the basal metabolic rate decreased regardless of sex and age. The perioperative changes correlated with the low-going growth hormone. **Conclusion:** Body composition and metabolism characteristics and the postoperative changes in acromegaly patients present an interesting and unique type. Different genders and age groups react differently. This type may aid to further explore the effect of growth hormone in the maintenance of substrate metabolism and body composition in human body.

*The authors have no relevant relationships to disclose.*
Pre-Surgical Peak GH Levels During GH Releasing Peptide (GHRP)-2 Test Sensitively Reflect The Severity of Hypopituitarism in Non-Functioning Pituitary Adenoma (NFPA)

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Objective: NFPA is one of the most common causes of hypopituitarism in adulthood. In this study, we investigated factors that predict the severity of hypopituitarism in patients with NFPA. Patients and Methods: Fifty patients who underwent transsphenoidal surgery for NFPA (M 26/F 24, age 60±14 years) were studied. Severity of hypopituitarism was evaluated by preoperative basal hormone levels and results of dynamic tests. GH secretory status was evaluated by GHRP-2 test. Patients were classified into three groups according to the severity of hypopituitarism as follows; normal group (gr. N), mild group (gr. M: 1 or 2 axis deficiency) and severe group (gr. S: 3 or 4 axis deficiency). Clinical manifestation, age, sex, BMI, tumor size and extension and the peak value of GH undertaking GHRP-2 test before surgery were investigated and compared among three groups. Results: There were no significant differences among gr. N (n=16), gr. M (n=23) and gr. S (n=11) in clinical manifestation, age, sex and BMI. Degrees of tumor extension evaluated by MRI findings did not predict the severity of hypopituitarism, though hyperprolactinemia was most frequent in gr. S (gr. N: 25%, M: 25% and S: 55%). Pre-surgical peak GH levels during GHRP-2 test were 26.7±16.5 ng/ml in gr. N, 8.9±7.1 ng/ml in gr. M and 1.8±1.1 ng/ml in gr. S. Conclusion: Among various factors studied, pre-surgical peak GH levels during GHRP-2 test reflected the severity of hypopituitarism most sensitively.

The authors have no relevant relationships to disclose.

Predictors of Surgical Cure in Acromegaly

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Introduction: Surgical cure in acromegaly can only be defined after 3 months and there are no robust pre-operative predictors or early criteria of cure. Aim: To analyze if clinical, radiological and biochemical features are predictors of surgical cure in acromegaly. Methods: Consecutive acromegaly patients submitted to surgery between 2013-2016 at a single center were included. All patients signed informed consent forms. GH and IGF-I levels were measured 24, 48 hours and one week after surgery. Tumor volume, signal in T2-weighted sequence and cavernous sinus invasion (defined according to Knosp-Steiner criteria) were evaluated in pre-operative sellar MRI. Tumor was considered hyperintense when the signal was ≥ adjacent grey matter. Results: Sixty-three patients were included (33 males). Median age at diagnosis was 46 years (14 – 78). Radiological classification was possible in 46 patients. Surgical cure was obtained in 31 patients (49.2%). Cure rates were not different between males and females and between hyperintense and iso/hypointense tumors. Surgical cure was obtained in 19 of 31 (61.3%) non-invasive tumors, while it was achieved in 4 of 15 (26.7%) invasive tumors (p=0.029). There was no difference in tumor volume or pre-operative GH or IGF-1 levels between those patients cured or not after surgery. GH levels after surgery were lower in cured patients in comparison with not cured ones 24 h [1.5 µg/L (0.4 – 8.6 µg/L) vs 7.4 µg/L (0.8 – 99.9 µg/L), respectively, p=0.001] and 48 h [1.0 µg/L (0.1 – 4.8 µg/L) vs 4.4 µg/L (0.4 – 40.0 µg/L), respectively, p=0.001] after surgery. A GH level <3.8 µg/L 24 h after surgery was able to distinguish cured patients with a sensitivity of 89% and a specificity of 77%. Conclusion: Cavernous sinus invasion was associated with a lower chance of surgical cure. GH levels 24 h after surgery can help in the early definition of surgical cure.

The authors have no relevant relationships to disclose.
P34
Radiological Characteristics of Upper Airway and the Correlation with Obstructive Sleep Apnea Hypopnea Syndrome in Patients with Treatment-naive Acromegaly
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Objective: To observe the morphological characteristics of upper airways in patients with treatment-naive acromegaly using computerized tomography (CT) and magnetic resonance imaging (MRI), and to explore the relationship with the obstructive sleep apnea hypopnea syndrome (OSAHS). Methods: Twenty-five newly diagnosed and untreated acromegaly patients were consecutively enrolled, and informed consents were obtained before enrollment. This study was approved by the Ethical Committee of Peking Union Medical College Hospital. All 25 patients underwent overnight polysomnography. CT and MRI for upper airway were performed in straight and extensive positions, respectively. Anteroposterior diameter, transversal diameter, cross-sectional area (CSA) and thickness of the lateral (TLPW) and posterior pharyngeal wall (TPPW) were measured in four transverse levels, including soft palate, uvula, tongue base and epiglottis levels. Thickness and CSA of soft palate and the thickness of uvula were measured in parasagittal reconstruction plane. Comparisons of qualitative and quantitative variables were analyzed using χ2 test and t-test respectively. Results: OSAHS were found in 13 patients (52%). There existed no significant differences between parameters in straight and extensive positions in both CT and MRI. Patients with OSAHS have increased thickness of soft palate (1.24 ± 0.22 vs 1.03 ± 0.22, cm, p=0.024), CSA of soft palate (5.15 ± 1.21 vs 4.06 ± 1.09, cm2, p=0.027) and thickness of TLPW (1.01 ± 0.25 vs 0.79 ± 0.14, cm, p=0.015), and decreased transversal diameter (1.87 ± 0.40 vs 2.31 ± 0.44, cm, p=0.015) and CSA (1.98 ± 0.46 vs 2.74 ± 1.01, cm2, p=0.032) on soft palate level in CT images. No differences were found between two groups using MRI. Conclusion: OSAHS were common in acromegalic patients, and were caused by thickened soft palate, thickened TLPW, decreased transversal diameter and CSA of upper airway on soft palate levels. Upper airway CT has predictive effect for this comorbidity.

The authors have no relevant relationships to disclose.

P35
Seniors with Acromegaly: A Descriptive Report From the Retrospective Acromedic Database
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Objective: We describe management of acromegaly and comorbidities in elderly patients at four geographically separate hospital systems in the US in recent years. Subjects and Methods: The AcroMEDIC database is comprised of data extracted from inpatient and outpatient electronic health records (EHR) of patients with acromegaly at four consortium hospital systems in the US, collected between the years 2003-2013 (Wash U and HFHS) or 2008-2013 (UMD and Baylor Scott & White). Chart review validated acromegaly in 35 patients (49% female) who were aged 71-89 at their first record. Statistics are descriptive. Results: Thirteen of 35 patients had at least one IGF-1 lab on record. Of these, 6 were biochemically controlled in all instances, 2 were brought into control, and 5 had IGF-1 values remaining above the normal range for age. Three patients had pituitary surgery during the years covered, none had radiotherapy, and 2 patients had records for acromegaly–specific drugs. Thirty elderly patients (86%) had no record of surgery, radiotherapy, or drug treatment for acromegaly during the years covered as opposed to 49% of those who were aged 70 or younger at first record. The most frequently recorded comorbidities were hypertension (49%), hypothyroidism (31%), diabetes mellitus (31%), hyperlipidemia (29%), and esophageal reflux (29%). When aggregated by category, elderly patients had more hypertension (57%, p=0.03), arthroalgia (31%, p=0.002), and cardiovascular (46%, p=0.03) comorbidity codes than those with acromegaly who were 70 or younger. Conclusions: Elderly patients with acromegaly have many of the same comorbidities recognized in the broader acromegaly population, however their frequency may be compounded by age. Relatively few were actively treated for acromegaly, possibly because they were surgically cured in years prior to our EHR capture.

Birol Emir, Janet Fox and Donna King are employees of Pfizer; Kashif Munir receives consulting fees from Pfizer; the other authors have no relevant relationships to disclose.
P36
Single-Center Experience of Patients with Acromegaly Treated with Long-Acting Pasireotide for at Least 5 Years
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Introduction: Pasireotide, a multiligand somatostatin receptor agonist approved for the treatment of acromegaly, demonstrated superior efficacy vs octreotide in treatment-naïve patients and in patients with uncontrolled acromegaly after treatment with lanreotide or octreotide. Clinical trials reported results up to 25 months; however, long-term tolerability, safety, and efficacy data are needed.

Methods: Single-institution experience of patients with acromegaly (C2305 Phase 3 study; NCT00600886) who were randomized to receive monthly pasireotide long-acting 40 mg intramuscularly and treated over 5 years is described. All patients completed the trial. OHSU institutional Review Board approved the study protocol.

Results: Three patients were treated with first-line pasireotide postoperatively for a mean duration of 6.2 years, including 1 patient diagnosed with multiple myeloma 2.7 years after study entry who was treated with chemotherapy. At baseline: mean insulin-like growth factor 1 (IGF-1) 2.4 x the upper limit of normal, and 5-point mean growth hormone (GH) 6.67 ng/mL. Post-operative MRI showed a residual tumor in each patient, with a mean ± SD maximum diameter of 8.3 ± 6.5 mm. After initiating pasireotide, IGF-1 normalized, and GH levels were reduced to <2.0 ng/mL within the first 3 months in all 3 patients. Stable or minimal regression of tumor volume was detected. Improvement in acromegaly-related symptoms, including joint pain, headaches, and sleep apnea, was noted. All patients experienced mild and intermittent diarrhea, but none experienced nausea. Hyperglycemia was noted in 2 patients and treated with metformin (500–2000 mg) and/or glipizide (2.5–5 mg) daily; glycated hemoglobin remained ≤6.8% at end of study.

Conclusions: This case series demonstrated successful adjuvant control of acromegaly in patients with multiple comorbidities after >5 years of pasireotide. Adverse events were tolerated and managed with oral medications as needed. These descriptive results support the long-term use of pasireotide in patients who receive early benefit.

Maria Fleseriu is a scientific consultant and principal investigator with research support to OHSU for Novartis, Chiasma, Cortendo and Pfizer; the other authors have no relevant relationships to disclose.

P12
Synchronous Pituitary Adenomas Causing Cushing Disease and Acromegaly
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Context: This case of both Cushing Disease and acromegaly due to distinct synchronous pituitary adenomas is the first report of two or more simultaneous adenomas with distinct histological and immunohistochemical (IHC) features confirmed with RT-PCR. Case Description: A 68yo woman presented for neuroendocrine evaluation, which revealed 2 elevated late-night salivary cortisols (7.6 and 5.7 nmol/L (≤4.3)), 5 normal 24-hour urine free cortisols, normal serum prolactin (PRL), elevated insulin-like growth factor-1 (IGF-1) (302 ng/mL (75-263)) and borderline growth hormone (GH) suppression on oral glucose tolerance test (OGTT) (nadir GH 1.0 ng/mL). MRI demonstrated a 20 x 17 x 9 mm left sellar lesion. Transsphenoidal surgery revealed an adenoma with IHC staining showing most tumor cells reactive for ACTH, rare staining for PRL, and negative staining for GH, betaTSH, betaFSH, betaLH, and alpha subunit. Post-operative adrenal insufficiency confirmed remission from Cushing Disease, but serum IGF-1 remained elevated (420 ng/mL (41-279)) with nadir GH 1.1 ng/mL on OGTT. Post-operative MRI showed a right sellar 6 x 5 x 3 mm lesion that appeared distinct from the left sellar lesion. Transsphenoidal surgery revealed an adenoma with IHC staining showing most tumor cells reactive for ACTH, rare staining for PRL, and negative staining for GH, betaTSH, betaFSH, betaLH, and alpha subunit. Post-operative adrenal insufficiency confirmed remission from Cushing Disease, but serum IGF-1 remained elevated (420 ng/mL (41-279)) with nadir GH 1.1 ng/mL on OGTT. Post-operative MRI showed a right sellar 6 x 5 x 3 mm lesion that appeared distinct from the left sellar lesion. A second transsphenoidal surgery revealed a second adenoma, with IHC staining demonstrating most tumor cells reactive for GH and betaFSH, many for PRL and alpha subunit, some for betaLH, rare for betaTSH and negative ACTH staining.

Discussion: Case reports of synchronous tumors have remained limited to IHC. This is the first report of synchronous functioning pituitary adenomas confirmed using differential RNA expression of ACTH and GH.

The authors have no relevant relationships to disclose.
The Many Faces of Acromegaly

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Objective: To characterize somatic differences in patients with acromegaly and correlate the findings with the recently proposed Structural and Functional Acromegaly Classification [1]. Materials and Methods: 150 acromegalic patients with morphologic diagnosis were included. They were categorized into several histological subtypes: tumors producing only GH (densely, sparsely and a mixture of both densely and sparsely granulated subgroup), tumors with prolactin and GH co-secretion, and plurihormonal tumors. Only pure GH-cell producing adenomas were considered for the study and they were classified as Type 1, Type 2 or Type 3 as previously proposed [1]. Photographs of the patient’s faces were analyzed by different observers and classified according to the acromegalic changes as strong, moderate and mild. These results were correlated with the morphologic subtypes using Fisher’s exact test and the accuracy of this clinical observation as a diagnostic test was measured. Results: a statistically significant correlation was found between the somatic changes in the faces of the patients and the histological subtype of the tumor. Sparsely granulated tumors produced milder somatic changes compared to densely granulated adenomas. This clinical observation may be used as a preliminary tool to predict the final histological diagnosis. Conclusion: using a heuristic approach, the face of the patient may reveal conclusive clues for prediction, diagnosis and correlation with the histologic subtype of the tumor and the Structural and Functional Acromegaly Classification.

P38

The Octreotide Suppression Test is Not Useful to Identify the Response of Acromegalic Patients to Somatostatin Ligands Therapy

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Introduction: Somatostatin receptor ligands (SRL) are considered as the first line medical therapy for most patients but not all respond to these drugs. The acute octreotide suppression test (OST - 100 µg of sc octreotide) role to predict the response to long-term treatment with SRL has been controversial in the literature. Objectives: To add data on the usefulness of OST for predicting patient’s response to SRL treatment. Methods: In a retrospective study, 21 acromegalic patients with active disease (absence of GH suppression below 0.4 ng/dL during OGTT-75g and elevated IGF-1 level) were submitted to OST before SRL therapy. The predictive values obtained during the OST were assessed by ROC curves. Results: GH drop greater than 93% during OST had a sensibility of 100% with a specificity of 83% for predicting hormonal control during SRL therapy. However, when assessing individual data patients can exhibit a substantial drop during OST without hormonal control on SRL, whereas others presented opposite situation (table 1).

Table 1. GH fall (%) during OST and IGF-1 levels before and during SRL therapy.

<table>
<thead>
<tr>
<th>Patients</th>
<th>GH fall (%)</th>
<th>Initial IGF-1 (xULNR)</th>
<th>Last IGF-1 (xULNR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-96.9</td>
<td>2.3</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>-94.1</td>
<td>1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>3</td>
<td>-96.1</td>
<td>1.3</td>
<td>0.9</td>
</tr>
<tr>
<td>4</td>
<td>-69.9</td>
<td>2.5</td>
<td>0.9</td>
</tr>
<tr>
<td>5</td>
<td>-82.5</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
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</tr>
<tr>
<td>11</td>
<td>-56.7</td>
<td>4.0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients</th>
<th>GH fall (%)</th>
<th>Initial IGF-1 (xULNR)</th>
<th>Last IGF-1 (xULNR)</th>
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<tr>
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<td>21</td>
<td>-71.5</td>
<td>3.5</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Conclusion: Although statistical analysis can provide OST cut-offs predicting the probability of SRL responsiveness when assessing individual data, this test can’t clearly exclude or indicate which patient will benefit from SRL therapy. The authors have no relevant relationships to disclose.
P39
Thyroid Diseases in Acromegaly: The First and the Largest Case Series in China
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*These authors contributed equally to this work.
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Objective: Acromegaly usually increases the risk of thyroid diseases. Yet data on the prevalence of benign and malignant thyroid disease in acromegalic patients remain controversial, mainly due to the tremendous differences in geographical and ethnic compositions. Although accounting for one-fifth of the world’s population, the exact prevalence of thyroid disease in acromegaly is still unknown in China. Therefore, the objective of our study was to investigate the clinical characteristics and risk factors related to thyroid diseases in acromegaly, using the first and by far the largest case series in China. Methods: Ninety-three acromegalic patients were recruited according to the inclusion and exclusion criteria, including 40 males and 53 females, aged 13–71 years. All patients underwent thyroid ultrasonography and were diagnosed with TI-RADS evaluation system. Linear regression analysis was used to detect the correlations between clinical data. Binary logistic regression analysis was used to identify related risk factors. This study was approved by the Ethical Committee of PUMCH. Results: The prevalence of thyroid diseases in acromegaly was 77.4% (74.2% benign, 3.2% malignant). Multiple linear regression analysis showed that thyroid volume was linearly correlated with random GH (p = 0.002), nadir GH (p = 0.005) and IGF-1 (p = 0.004), T3 level was linear with IGF-1 (p < 0.05). The group with thyroid-diseases had higher GH burden (p < 0.05) than normal group. Multivariate logistic regression analysis showed that age was an independent risk factor for thyroid diseases in acromegaly (p = 0.002). Conclusion: Compared with normal population, the risk of thyroid diseases is significantly higher in acromegaly, which is closely related to GH, IGF-1 and age of onset. We suggest that thyroid ultrasonography should be performed once the diagnosis of acromegaly was made. The reduction of GH burden is of vital importance in the treatment of thyroid diseases in acromegaly.

The authors have no relevant relationships to disclose.

P40
Treatment of Patients with Acromegaly and Inadequate Biochemical Response or Intolerance to First-Generation Somatostatin Receptor Ligands: A Single-Center Experience
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Introduction: Pegvisomant, long-acting pasireotide, or combination medical therapy are available options for 35%–60% of patients for whom biochemical control is not achieved with first-generation somatostatin receptor ligands (SRLs). To inform selection of second-line therapy, this analysis presents results from a single-center experience of patients for whom first-generation SRLs failed. Methods: IRB-approved retrospective analysis of medical records of all patients with acromegaly treated at OHSU between 2006 and 2016 who had inadequate response or intolerance to high doses of first-generation SRLs (lanreotide 120 mg or octreotide LAR 30 mg). Results: Twenty-five patients (uncontrolled acromegaly, n=21; SRL-intolerant, n=4) were included in the analysis. Among patients with uncontrolled acromegaly, insulin-like growth factor 1 (IGF-1) levels normalized in 64% (7/11) of patients treated with SRL + pegvisomant (30–120 mg/week), 80% (4/5) treated with pegvisomant monotherapy (90–280 mg/week), 75% (3/4) treated with pasireotide (40–60 mg/month), and 100% (1/1) treated with SRLs + cabergoline (1 mg/week). Four patients on SRL + pegvisomant (30–140 mg/week) switched to pasireotide (40 mg/month): 2 patients with uncontrolled disease, and 2 patients with controlled acromegaly (1 developed injection-site lipodystrophy, 1 preferred to minimize injections). Of these four, 75% achieved normal IGF-1 on third-line pasireotide. Among the four patients who switched from SRLs due to adverse events (hypoglycemia, n=2; diarrhea, n=2), three (75%) achieved normal IGF-1 after switching to pegvisomant monotherapy (70 mg/week), pegvisomant (70 mg/week) + cabergoline (1 mg/week), or low-dose SRL + pegvisomant (60 mg/week). Conclusions: In the past 10 years, adding or switching to pegvisomant was most commonly used and effective in 66% of patients with acromegaly with inadequate response or intolerance to first-generation SRLs. Pasireotide, a second-generation SRL, is also a viable therapeutic and convenient option for selected patients with uncontrolled acromegaly on SRL + pegvisomant or patients who experience pegvisomant-related adverse events.

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P41
A Randomized Controlled Trial of an Educational Website on the Medical and Surgical Knowledge of Patients with a Pituitary Adenoma

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Objective: Determine the medical, surgical procedural, health-care system and self-perceived knowledge gained from a pituitary adenoma informational website created by a multi-disciplinary team. Methods: After a needs assessment and determining gaps in pituitary tumor knowledge, we gathered relevant information to create an educational website. Upon referral to our multidisciplinary clinic for pituitary-related care, patients were randomly assigned to receive access to our website or simply allowed to seek out information on their own. Of the 41 patients who completed the study, 19 received this link, 22 did not. Three questionnaires were created, Pre-, Post I- and Post II-exposure, which tested patient literacy around pituitary tumours and their management. The Pre-questionnaire was given before visiting the specialist without receiving educational materials. The Post I-exposure questionnaire was given after completion of the Pre-questionnaire with (intervention group) or without (control group) receiving educational materials. The Post II-exposure questionnaire was given 3–6 weeks after visiting their specialist.

Results: The intervention group had significantly higher medical knowledge than the control group in the Post I- and II-questionnaires. In the intervention and control groups, self-perceived knowledge score significantly increased from Pre to Post II-questionnaires, while surgical knowledge score significantly increased from Pre to Post I- and II-questionnaires.

Conclusion: This educational resource for patients with pituitary disorders increased participants’ medical knowledge of pituitary disorders and their management.

The authors have no relevant relationships to disclose.

P42
Atypical Pituitary Adenomas: A Systematic Literature Review and Comment on Standardization of Diagnosis

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¹Department of Neurosurgery; ²Division of Neuropathology, Department of Pathology; ³Division of Endocrinology, Department of Medicine; ⁴USC Pituitary Center, Keck School of Medicine of USC, Los Angeles, California, USA

Context: Atypical pituitary adenomas (APAs) are a subset of pituitary adenomas (PAs) characterized by the WHO to have higher risk histopathological features than typical PAs. To date, no systematic meta-analysis pertaining to the prevalence and clinical characteristics of APAs has been published. Objective: We reviewed the literature to describe the prevalence of APAs and associated clinical courses. We then comment on potential issues in standardized application of WHO criteria. Study Selection: A systematic review identified studies reporting prevalence and clinical characteristics of APA according to PRISMA guidelines. Initial keyword search produced 355 abstracts, of which 193 abstracts met pre-specified inclusion and exclusion criteria. After full review, seven studies were included for analysis, containing data on 1,264 patients. Five studies reporting histopathological details were included in the meta-analysis. Two independent reviewers determined the quality of studies and extracted data from the PubMed database (2004-November 2016) regarding prevalence, outcome, clinical, histopathological, and imaging characteristics. Data Synthesis: Of the 1,264 included patients, 173 patients (5.3%) met criteria for APA (range: 3–15%). The average MIB-1/Ki-67 LI was 5.34% (mean range: 3-7%, overall range: 3-25%). Invasion on neuroimaging was reported in 35% of APA patients. Nonfunctional PAs were the most common pathological subtype (45%), followed by GH-secreting PAs (20%) and prolactinomas (18%). Recurrence/progression occurred in 19% of APA patients over follow-up (range 37–75 months). Only 2/8 studies used identical grading criteria, demonstrating a potential lack of standardization.

Conclusions: The prevalence of APAs among surgically-treated PAs is 5.3%. The 2004 WHO guidelines for APA diagnosis provide a starting point to assess the prevalence and treatment response in APA patients. Based on the insights obtained during the past decade of research, reevaluation and refinement for more consistent application of the 2004 WHO diagnostic criteria may improve future understanding of this relatively heterogeneous disease entity.

The authors have no relevant relationships to disclose.
P43
Atypical Pituitary Adenomas: Prevalence and Diagnostic Challenges at a Tertiary Pituitary Center
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1Department of Neurosurgery; 2Division of Neuropathology, Department of Pathology; 3Division of Neuroradiology, Department of Radiology; 4Division of Endocrinology, Department of Medicine; 5USC Pituitary Center, Keck School of Medicine of USC, Los Angeles, California, USA

Objective: Few reports pertaining to the incidence and clinical implications of atypical pituitary adenomas (APA) have been published. We aimed to retrospectively review the incidence of APA as well as imaging, pathological and clinical features of APA at a tertiary referral center for pituitary disease.

Methods: The records of 171 consecutive patients who underwent endoscopic endonasal transsphenoidal surgery for pituitary adenomas between 2011-2016 at Keck Hospital of USC were retrospectively reviewed for having a pathological diagnosis of APA. Results: APA was diagnosed in 9 of 171 patients (5.3%). The mean patient age was 51 years (range 30-62 years). 5 patients had nonfunctional tumors (56%), 2 had acromegaly (22%), 1 had central hyperthyroidism (11%), and 1 a prolactinoma (11%). All 9 APAs were macroadenomas with a mean maximal diameter of 23 mm. Of these, 5/9 (56%) demonstrated evidence of extrasellar invasion. Gross total resection (GTR) was performed on 6 patients (67%) and subtotal resection (STR) on 3 (33%). Histological and immunohistochemical features of APAs included a mean Ki-67 labeling index of 3.9% (range 1.9 – 7.0%), nuclear immunoreactivity for p53 (all patients), and elevated mitotic indices (5/9, 56%). APA immunohistological subtypes included null cell adenoma (3/9, 33%), thyrotroph adenoma (3/9, 33%), somatotroph adenoma (2/9, 22%) and prolactinoma (1/9, 11%). No APA patients had tumor recurrence or progression over the mean follow-up time of 15 months. Conclusion: The prevalence of APA was 5.3% ranging over five years. The majority of the APAs were invasive macroadenomas consisting of silent and functional PAs, often with plurihormonal or null-cell immunostaining. Refinement of the APA criteria and incorporation of the APA designation into a predictive model including key clinical, hormonal and imaging criteria may offer a higher predictive potential to identify patients at higher risk.

The authors have no relevant relationships to disclose.

P44
Diaphragma Sellotomy: A Safe Technique to Confirm Adequate Decompression of Optic Chiasm
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1Department of Neurosurgery, Loma Linda University Medical Center, Loma Linda, CA, USA; 2Loma Linda University School of Medicine, Loma Linda, CA, USA

Objective: Optic chiasm decompression for preservation or restoration of vision is often the primary surgical goal for patients with pituitary macroadenomas. Descent of the diaphragma sellae (DS) is a surrogate marker of adequate chiasm decompression. However, DS is not always readily identifiable and its descent not always symmetric. Intraoperative MRI (iMRI) has become an increasingly utilized, though cost-prohibitive tool to confirm decompression. We propose a technique of intentionally incising the DS to ensure adequate chiasm decompression.

Methods: Patients with pituitary non-prolactin secreting adenomas causing profound visual deterioration underwent transphenoidal surgery and DS incision when the DS was not easily identified and/or did not descend. The < 3mm incision allowed for direct visualization of the suprasellar cistern and optic chiasm. CSF leak was repaired using a naso-septal flap in 4 cases intradural dural substitute and thrombin glue in another case. Results: 5 patients (2 females and 3 males, average age: 48.6, age range: 18-69, average BMI: 29.02 kg/m2) with pituitary macroadenomas (average size: 6.4 cm3) had endoscopic endonasal transphenoidal resection. Vision improved in all cases postoperatively. There were no postoperative complications or CSF leaks at 1 year. Conclusion: Diaphragma sellotomy ensures chiasm decompression with minimal risk to the patient with current reconstructive techniques and without the need for iMRI. Repeat immediate or delayed surgery to ensure chiasm decompression can be avoided. This may allow for more rapid recovery of vision.

The authors have no relevant relationships to disclose.
P45
Differences in Post-operative Sino-Nasal Quality of Life Between Microscopic Trans-sphenoidal and Endonasal Endoscopic Surgery for Pituitary Adenomas

Manju Dhandapani1, Priyanka Prakash1, Sandhya Gupta2, Sivashanmugam Dhandapani1, Manju Mohanty1, Sunil K Gupta3, Roshan Verma4, Pinaki Dutta5, Kanchan K Mukherjee1

1NINE, PGIMER, Chandigarh, India; 2CON, AIIMS, New Delhi, India; 1Dept. of Neurosurgery, PGIMER, Chandigarh, India; 1Dept. of ENT, PGIMER, Chandigarh, India; 5Dept. of Endocrinology, PGIMER, Chandigarh, India

Objective: The study was conducted to assess the post-operative sino-nasal quality of life of patients who underwent microscopic or endoscopic trans-sphenoidal surgery for pituitary macroadenomas, and evaluate factors influencing it.

Methods: Using consecutive sampling, patients with non-giant pituitary macroadenomas having no pre-existing nasal complaints, who underwent transsphenoidal surgery, were included for the study after IEC approval. Sino-nasal quality of life was assessed at 3 to 6 months after surgery using Sino-nasal outcome test (SNOT-22) which is a 22-item questionnaire having a score range of 0 to 110. A high score indicates poor quality of life. This was studied in relation to other clinico-radiological factors. Non-parametric tests were carried out using SPSS 21.

Findings: 25 patients who consented for the study were enrolled. Out of 25 patients, 13 patients underwent endonasal endoscopic surgery and 12 underwent microscopic approach. The median SNOT-22 score overall was 24 [IQR 6-29]. The most frequent complaints included reduced productivity (32%), reduced concentration (28%), fatigue (28%) and reduced sleep (20%). SNOT-22 score was significantly lower among patients who underwent endonasal endoscopic approach (median 18 [IQR 2-25]), compared to patients who underwent microscopic approach (median 26 [IQR 18.5-36]) (p=0.05). None of the other factors analyzed had any significant association with sino-nasal quality of life.

Conclusions: Post-operative sino-nasal quality of life is significantly better following endonasal endoscopic surgery compared to microscopic trans-sphenoidal surgery in patients with pituitary adenomas.

The authors have no relevant relationships to disclose.

P46
Exome Sequencing of Acromegaly and Cushing - What’s New?

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Introduction: Advent of massively parallel DNA sequencing methods has revolutionized cancer genome sequencing. Efforts to sequence whole genomes/whole exomes to map genetic anomalies in different types of pituitary adenomas have been limited. Candidate gene based sequencing has revealed mutations, which include GNAS, MEN1, aryl hydrocarbon receptor interacting protein (AIP), and ubiquitin specific peptidase 8 (USP8). Objective: Whole exome sequencing of somatotropinomas and Cushing. Methodology: Exome sequencing was performed on familial (n=6) as well as young sporadic (n=12) cases of somatotropinomas and Cushing (n=22). All the cases were paired samples i.e. germline and somatic. The samples were sequenced at an average depth of 130x. This study was approved by Institute Ethics Committee. Results: In Cushing, we identified over 100 mutations including USP8, nuclear receptor subfamily 3 group C member 1 (NR3C1), chromodomain helicase DNA binding protein 2 (CHD2), ubiquitin specific peptidase 29 (USP29), and MEN1 which have been previously reported. We identified nearly 100 mutations that have not been reported before including frameshift mutations in methyl-CpG-binding domain protein 5 (MBD5), cut like homeobox 2 (CUX2) and proline rich 12 (PRR12). In somatotropinomas, as expected we identified recurrent mutations in GNAS. We did not identify AIP mutations in most cases of acromegaly including familial that has been found to be relatively frequent among somatotropinomas. We identified over 60 mutations that have not been reported in acromegaly. This includes cell division cycle 27 (CDC27) that was recurrent and several genes that were mutated only in one of the sequenced tumors. Conclusion: We identified novel recurrent frameshift mutations in MBD5, CUX2 and PRR12 in Cushing. CDC27 was recurrent among the 60 novel identified mutations in somatotropinomas.

The authors have no relevant relationships to disclose.
Factors Influencing Bone Mineral Density & Osteoporosis in Patients with Acromegaly

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**Background & Objective:** Growth hormone (GH) is known to have anabolic effect on bone metabolism. However, long-term consequences of GH excess on bone are not clear. This study aimed to assess the prevalence of osteoporosis in acromegaly patients in relation to various factors. **Methods:** This was a cohort study on 50 patients of acromegaly (on calcium & vitamin D supplements) and 50 matched healthy volunteers less than 60 years after IEC approval. Acromegalic status was determined using serum GH and Insulin Growth Factor-1 (IGF-1). DEXA (Dual Energy X Ray Absorptiometry) scan was used for the evaluation of Bone Mineral Density (BMD) and studied in relation to age, gender, body mass index (BMI), biochemical (calcium, vitamin-D) and other hormonal markers (cortisol, testosterone, estrogen, parathormone (PTH)). WHO definitions were used for the diagnosis of osteoporosis (T-score < -2.5) and osteopenia (T-score between -2.5 and -1). Non-parametric tests were performed for various statistical analyses. **Results:** There was no significant difference in the prevalence of osteoporosis (18% vs 12%) or between the bone mineral density values (median 0.95 vs 0.95 g/cm²) between acromegaly patients and matched controls. Among acromegaly patients, BMD showed significant rank-order correlation with BMI (ρ=0.39, p=0.01). Patients with T-score less than -1 had significantly lower BMI compared to those with T-score better than -1 (median 24.98 vs 28.29 Kg/m²). In hormone profile, serum testosterone showed significant positive rank-order correlation (ρ=0.34, p=0.03), while PTH had significant inverse rank-order correlation (ρ=0.39, p=0.01) with BMD values. PTH levels were significantly higher among acromegaly patients with osteoporosis compared to those without osteoporosis (median 64.55 vs 37.21, p=0.01). Other factors including GH and IGF-1 did not show significant impact on BMD values. **Conclusion:** Acromegaly per se does not seem to increase the risk of osteoporosis. BMI, testosterone and PTH levels have significant correlation with BMD and osteoporosis in patients with acromegaly.

The authors have no relevant relationships to disclose.

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Loss of Expression of Kisspeptin/KISS1R Genes in Somatotropinomas and Nonfunctioning Pituitary Tumors

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The expression of the kisspeptin 1 (KISS1) and its receptor (KISS1R), both involved in tumor suppression, have recently been reported in pituitary adenomas (1, 2), but their relationship with pituitary tumorigenesis/progression remains uncertain. To study the impact of the kisspeptin/KISS1R system in pituitary tumors, we assessed KISS1 and KISS1R mRNA levels of 60 tumor samples (37 somatotropinomas and 23 nonfunctioning pituitary adenomas/NFPA) using real-time PCR relative quantification (RQ) with TaqMan® assays. The categorical data were expressed as percentages and compared by Chi-square test using Sigma Stat. P<0.05 was considered statistically significant. This study was approved by the local Ethics Committee. KISS1 was found to be underexpressed in relation to the normal control pool (RQ<0.5) in 91% of these samples, regardless tumor subtype. KISS1R was also mostly underexpressed or absent (82% and 8% of all tumors, respectively), while 5% of the samples had normal levels of expression, and the remaining 5% had this gene overexpressed (RQ>2). Our data adds to what was previously reported in qualitative experiments, where expression of KISS1 or KISS1R was found in roughly half of the samples and in another study KISS1 could not be detected and KISS1R was found to be preferably expressed in NFPA. Together, these findings suggest that expression of the kisspeptin/KISS1R system is lost early in the pituitary tumorigenesis, possibly representing a major episode in the development of this disease. In conclusion, we speculate that the KISS1-KISS1R genes may contribute to the pituitary tumorigenesis. Also, as expression of this receptor is conserved in a portion of the subjects, this system could represent a novel therapeutic target for patients with pituitary adenomas. However, additional studies with larger samples are required to confirm these findings.

The authors have no relevant relationships to disclose.
P49
Open for Discussion: How to Proceed Towards a Value Based Health Care Integrated Practice Unit for Pituitary Adenoma Patients

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Background: The outcome of patients with pituitary tumors is highly variable, but on average long-term mortality is increased, and physical and psychosocial impairments persist despite state of the art treatment. Unfortunately, literature data have limitations in providing prognostic data for decision making today, because of the small size and heterogeneity of patients, combined exposures, lack of randomized studies, and ongoing innovations in pituitary care. The value base health care (VBHC) principle by Porter evaluates care as delivered today and added value of treatments. We describe our ongoing efforts to improve care of pituitary disease at maximal added value/ optimal cost to open the discussion how to shape future pituitary care.

Approach: The long-term clinical outcome data of our center have been extensively evaluated since the start of dedicated transphenoidal surgery from the late 1970s, including data on mortality, morbidity, quality of life, patients' perception, bother and needs. Today's patients' expectations and social outcome are currently being evaluated. Our pituitary practice was extensively discussed and adjusted accordingly using previous data, literature evidence and expert opinion. Identified processes of special interest were referral and planning of first visit, perioperative care, and evaluating the need for chronic care. Patient centred care was detailed for all health care providers with task description and proposed outcome parameters. The following adjustments were made: first visit: personalized intake, weekly multidisciplinary clinic and team meetings; perioperative period: pre-and post-operative multidisciplinary counselling to fine-tune patient management; improved surgical decision making through team surgery, increased self-care in early discharge if uncomplicated procedure; chronic care: use of bother and need questionnaire, self management education program. Monthly evaluation of the process and patient outcomes (PDCA cycle) are anticipated. The ultimate aim is to provide short time evidence for improved patient outcomes and patient satisfaction, at a time- and cost-efficient fashion.

The authors have no relevant relationships to disclose.

P50
Pituicytoma Associated with Acromegaly and Cushing Disease: Report of Two Cases

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Introduction: Pituitary adenomas can occur with other sellar pathologies, and the term collision sellar lesions has been coined for this rare entity.1 Pituicytoma is a rare neoplasm arising in the sellar region (WHO grade I). Clinically, pituicytomas mimic nonfunctioning pituitary macroadenomas, and are occasionally incidentally discovered at autopsy.2 There have only been a few reports of the coexistence of pituicytoma and pituitary adenoma.3 Here we present two cases of pituicytoma coexisting with acromegaly and Cushing disease.

Case report 1: 33-year-old woman with ACTH dependent Cushing disease. The patient underwent endonasal resection. Undetectable postoperative cortisol levels provided evidence that the underlying ACTH-source was successfully removed. Based on the morphologic features and immunohistochemical profile, pituicytoma was diagnosed on pathologic examination. The pituitary adenoma was not confirmed histologically in this patient. Case report 2: 29-year-old woman with acromegaly. The macroadenoma was partially removed in the first surgery, thus endonasal re-operation was required for debulking and posterior radiosurgery. Pituicytoma coexisting with somatotropinoma was diagnosed on pathologic examination. Discussion: Only 78 cases of pituicytoma have been reported since it was first described in 1955. Before our reports only five cases of patients with pituicytoma coexisting with pituitary adenoma had been described. The coexistence of these two entities may not just be a mere coincidence, but may be due to a yet unknown pathophysiological link or common progenitor lineage of both lesions. Neidert et al. hypothesized that the coexistence of these 2 lesions is underdiagnosed as, in only very few cases, the neuropathologist is provided with enough tissue sample containing both lesions.4 Conclusion: Association between pituicytoma and pituitary adenoma is increasingly being reported. References: 1Koutourousiou et al. Pituitary 2010. 2Yang X et al. Oncol Lett. 2016. 3Neidert et al. Hum Pathol. 2016. 4Neidert et al. Hum Pathol. 2016 (correspondence).

The authors have no relevant relationships to disclose.
P51
Presentation, Treatment, and Long-term Outcome of Intrasellar Chordoma
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Purpose: Chordoma is a locally aggressive tumor arising from notochord remnants along the neuraxis. The purpose of this study was to determine common features, treatment approaches and survival characteristics of intrasellar chordoma. Methods: Institutional databases at BWH/MGH were searched for intrasellar chordoma. The Surveillance, Epidemiology, and End Results (SEER) database November 2015 submission was queried for ‘chordoma’ (ICD-O-3 9370/3) occurring primarily in the ‘pituitary gland’ (Site C75.1). Using PubMed/NCBI, a literature review of intrasellar chordoma was conducted. Chondroid chordoma, a less aggressive chordoma variant was included in all searches. Patient-level data was extracted where available. Kaplan-Meier statistical analyses were conducted with a primary endpoint of death to compare factors contributing to survival (p<0.05 threshold for significance). Results: A total of 89 cases were evaluated, of which 8 were a chondroid variant. The mean age at presentation was 55 (SD ± 15.8), with a slight female predilection (1.1:1). Patients experienced symptoms for 19.3 months, including neurological (92 percent) and endocrine (44 percent) disturbances. Common abnormalities included vision loss, headache, hyperprolactinemia, and hypopituitarism. Among patients receiving treatment, 88.6 percent underwent surgery, 52.4 percent with a transsphenoidal or endonasal approach and 47.6 percent with a craniotomy. Adjuvant radiation was utilized in 45 percent of patients. The 5-year overall survival rate was 60.8 percent. Patients aged 40 and younger had a 5-year overall survival rate of 83.1 percent, compared to 55.7 percent in patients older than 40 (Mantel-Cox, p=0.027). Adjuvant radiation did not change survival rate (Mantel-Cox, p=0.48). Conclusions: Intrasellar chordoma presents frequently with visual disturbances and hyperprolactinemia. It has an overall survival rate similar to intracranial chordoma. Unlike intracranial chordoma, overall survival in intrasellar chordoma is not improved with adjuvant radiation. External radiation may still offer the benefit of symptomatic control for intrasellar chordoma on a case-by-case basis.

The authors have no relevant relationships to disclose.

P52
Review for Failed Reconstruction Cases After Extended Trans-Sphenoidal Approach
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Objective: Extended trans-sphenoidal approach for the surgical management of suprasellar lesion is associated with a higher risk of cerebral spinal fluid (CSF) leakage and other related complications. Reconstruction of the skull base during surgery has become the key to success of this surgical approach. Methods: A retrospective study of all patients who underwent extended trans-sphenoidal surgery at Peking Union Medical College Hospital from 2009.6~2012.12 identified 3 patients who experienced symptoms of CSF leakage between 7~14 days after first surgery and was requiring re-operation. All 3 patients had substantial intraoperative CSF leakage as a result of the bony and dural defects in skull base, which was repaired by the multilayer skull base reconstruction method. Cause of the failure in reconstruction was revealed in the second operation. Results: 2 patients had successful repair and recovery after the second operation, following up in the later 6 months to 2 years did not reveal CSF leakage any more. The other patient continued to have CSF leakage after being re-operated. He developed intracranial infection, hemorrhage, and later resulted in death of the patient. Conclusions: The method of multilayer skull base reconstruction with autografted fascia lata could effectively reconstruct the skull base during extended trans-sphenoidal surgery for suprasellar lesion. Special attention should be paid to make the autografted fascia and iodoform gauze large enough and compress the defect securely. Factors predisposing to failure in reconstruction include hydrocephalous, ventricle enlargement, and intracranial hypertension.

The authors have no relevant relationships to disclose.
Safe Surgical Decompression is the Priority in Treating Granular Cell Tumor of the Sellar Region

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Purpose: Granular cell tumor (GCT) is a rare, predominantly benign neoplasm that can occur in the sellar region. The purpose of this study was to determine common presenting features, management approaches and the long-term outcome of GCT of the sellar region. Methods: Institutional neuropathology databases at BWH/MGH were searched for GCT of the sellar region. The Surveillance, Epidemiology, and End Results (SEER) database November 2015 submission was queried for ‘granular cell tumor of the sellar region’ (ICD-O-3 9582). Using PubMed/NCBI, a comprehensive literature review was conducted. Patient-level data was extracted where available. With a primary endpoint of recurrence, Kaplan-Meier analysis was performed to determine progression-free survival (PFS). (p< 0.05 threshold for significance). Results: A total of 141 cases were assessed. GCT of the sellar region occurs at a mean age of 48.9 (SD ± 15.3), with a higher tendency in females (1.5:1). Abnormalities included vision loss (68.3 percent), headache (24.7 percent), hyperprolactinemia (19.8 percent) and hypopituitarism (9.9 percent). The average tumor size was 2.7 cm. Preoperative diagnoses included adenoma, craniopharyngioma and meningioma. Among patients who underwent surgery, 46.4 percent were treated with a craniotomy and 33.0 percent were treated with a transphenoidal/endonasal approach. Additionally, 24.5 percent of patients received adjuvant radiation. GCT of the sellar region has a 5-year progression-free survival (PFS) of 87.1 percent. Adjuvant radiation lowered PFS (Mantel-Cox, p=0.001). PFS after gross-total resection (GTR) and subtotal resection (STR) did not differ (Mantel-Cox, p=0.14). The use of post-operative hormone replacement was not different between GTR and STR (Pearson Chi-Square, p=0.99). Conclusions: GCT of the sellar region recurs infrequently. PFS and need for hormone replacement therapy did not differ by surgical result. Therefore, emphasis should be placed on decompression and preservation of neurological functions. Adjuvant radiation reduced PFS, although this result could be due to insufficient data, requiring further research.

The authors have no relevant relationships to disclose.

Socioeconomic Status and Survival in Patients with Pituitary Tumors in the Census-tract Linked Database from the Surveillance, Epidemiology, and End Results (SEER) Program at the National Cancer Institute

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Disparities in survival associated with socioeconomic status (SES) have been identified in many tumors. The SEER program at the National Cancer Institute uniquely links patient outcomes with census-tracked SES variables. The cohort of patients with pituitary tumors has never been described in this database.

All patients diagnosed with a pituitary tumor between 2003 and 2012, and registered in the SEER database, were analyzed as part of this study. Treatment received included surgery, radiation, or radiation with surgery. SES was divided into tertiles (T1, T2, T3) with T1 being the lowest SES tertile. Logistic regression and Cox proportional hazards models were used to analyze data with SAS v9.4.

The study found that the SEER database included 85 patients diagnosed with a pituitary tumor. Average age at diagnosis was 51.03 ± 1.83 years. 50.59% patients were female. 70.59% patients were Caucasian, 17.65% were African American, and 11.76% were of other races. 35.39% patients were in T1 SES, 30.59% patients were in T2, and 34.12% in T3. 53.03% patients received surgery, 17.72% received radiation, and 11.76% received radiation with surgery. Mean survival time in this cohort was 31.81 ± 1.14 years with 89.41% survival at 5 years. There were no significant associations between survival probability and SES, race, or treatment received.

This analysis of a unique national cancer registry from the SEER program found a population of patients with pituitary tumors with several characteristics in line with previously published single-institution studies. In addition, it sheds new light on socioeconomic factors, rates of surgery and radiation, and overall survival in this population.

The authors have no relevant relationships to disclose.
P55
Temozolomide for Refractory Pituitary Adenomas or Carcinomas: A Single Center Experience
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Purpose: Refractory pituitary adenomas (RPAs) are recently proposed to define invasive-aggressive tumors with high Ki-67 indexes, exhibit aggressive behaviors, such as rapid growth, early and frequent recurrence, and resistance to conventional treatment, even in the absence of metastasis, with which are defined as pituitary carcinoma (PC). Temozolomide (TMZ) is an oral alkylating agent to treat RPAs and PCs. The purpose of this study was to summarize results of 21 patients with RPAs or PCs after TMZ treatment in a single pituitary center. Methods: Retrospective review of data extracted from clinical files. 21 patients were included into the analysis. Results: There were 9 nonfunctional PAs (NFPAs), 3 GH-secreting PAs, 4 ACTH-secreting Pas, 3 PRL-secreting PAs, and 1 PRL-secreting PC. All the PAs included met the criterion of RPAs. Mean age to start TMZ treatment was 53.3 ± 2.5 years. Median follow-up time was 25.9 months. 15 patients (71.4%) had disease control during treatment, while 6 patients (28.6%) had disease progression. In the 9 NPFAs, 4 patients had significantly tumor size decrease, 2 had stable disease and 3 had progressive disease. In the 3 GH-secreting PAs, 2 patients had significantly tumor size decrease and GH improvement while 1 had progressive disease. In the 4 ACTH-secreting PAs, 1 patient had significantly ACTH normalization, 1 had improvement while 2 had progressive disease. Interestingly, all the 3 PRL-secreting PAs, and 1 PRL pituitary carcinoma had significantly tumor size decrease and PRL improvement. 3 patients in 6 patients who stopped treatment had tumor re-growth. And the drug is well tolerated with few severe adverse effects. Conclusions: TMZ is effective and safe for the RPAs and PCs which are refractory to conventional therapies.

The authors have no relevant relationships to disclose.

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P56
The Diagnosis and Therapy of Pituitary Metastasis
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Object: To summarize the diagnosis, therapy and prognosis of pituitary metastasis. Methods: 10 cases from the department of neurosurgery of Peking Union Medical College Hospital (PUMCH) were analyzed retrospectively from Apr. 1997 to Aug. 2014. Results: There are 7 males (70%) and 3 females (30%), and the average age is about 60.4 years old. The clinical features were visual disabilities (50%). The postoperative pathological results reported that 1 case (10%) was metastasis of large cell lung carcinoma, 2 cases (20%) were metastasis of renal carcinoma, and 5 cases (50%) were metastasis of lung adenocarcinoma. All cases were thoroughly followed-up except for 1 case; the average survival time was 144 days. Conclusion: Pituitary metastasis was a rare disease. The diagnosis of the disease mainly depends on clinical manifestation and radiology. The main therapy method was operation. The prognosis of this disease is bad.

The authors have no relevant relationships to disclose.
P57
The Establishment of China Pituitary Disease Register Network
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Purpose: China is the most populous country and has the largest number of clinical cases of pituitary diseases in the world, however, the collection of clinical data is very weak, and lag far behind the developed country. To obtain the complete information on Chinese patients with pituitary disease, this project was to provide a perfect medical database and information sharing system for clinical data collection, further raise people's attention to the collection of clinical information. Methods: The first China Pituitary Disease Register Network was established by Peking Union Medical Hospital in 2015, and most pituitary disease institution in China was encouraged to register the information of patients with pituitary disease and share the information. Results: To date, there were more than 11000 cases of pituitary tumors were collected from 34 famous hospitals in China. In this database, there are more than 1600 case of Cushing disease, to our knowledge; this is the largest database on in the world. Based on this database, several clinical trials have been carried out and some papers published. Big data on Chinese pituitary disease has been obtained, which filled the gaps of the pituitary disease epidemiology in the world, because China is the most populous country in the world. These precious data has provided solid evidences for the writing of expert consensus and guidelines for assessment and treatment of pituitary disease for Chinese. We are going to carry out several nationwide multicenter clinical studies and epidemiological investigation. Conclusions: China pituitary disease register network is the first multicenter database for pituitary diseases in China, and it provides the most widely used platform for collection and sharing of data on pituitary disease in China. The big data from this platform is very important for multicenter clinical studies, epidemiological investigation, and writing of expert consensus and guidelines for assessment and treatment of pituitary disease.

The authors have no relevant relationships to disclose.

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P58
Tumor Volume Reduction after Temozolomide Treatment in Eight Patients with Non-functioning Pituitary Adenomas: A Single-center Experience
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Background: Although most pituitary adenomas are considered benign tumors some of them show aggressive phenotypes in their clinical course. These types of tumors generally need multimodal treatment. The efficacy of chemotherapy has been described in the treatment for aggressive pituitary tumors. Patients and Methods: We present here our experience with the use of temozolomide in eight patients with non-functioning pituitary tumors, three females and five males age range 22-72 y. All presented macroadenomas and all had unsuccessfull previous pituitary surgery (1-3 times) and conventional radiotherapy in five patients. In none of them extrapituitary presence of tumor was found. The tumors were defined as aggressive based on the radiologic criteria, lack of response to standard therapy and positive ki-67 immunostaining. Tumor volume was evaluated with magnetic resonance imaging using high-field MRI examination (>1.5 Tesla). Tumor specimen blocks underwent immunohistochemical studies, analysis of antibody that binds ki-67 antigen and p53 immunoreactivity. We did not perform immunoeexpression for MGMT. Immunostaining studies demonstrated a null-cell adenoma in three cases with oncocytic changes in one of them. In three other cases the study revealed a plurihormonal cell adenoma and in other case the specimen was not available. Temozolomide was administered in a dose regimen between 150-200 mg/m2 for a 5 of 28-day cycle (6 to 12 cycles completed). Results: After temozolomide treatment tumor disappearance was seen in one case (12.5%), tumor volume reduction of more than 20% was observed in five cases (62.5%) and only in one case tumor growth occurred. In one case the drug was stopped because of severe gastrointestinal intolerance. Conclusions: We conclude that medical therapy with temozolomide is well tolerated and can be helpful to reduce tumor volume in non-functioning pituitary tumors that fail to respond to conventional treatment. It may be considered earlier to decrease morbidity and improved outcome.

The authors have no relevant relationships to disclose.
P59
A Rare Case Presentation of Recurring Granulomatous Hypophysitis of Unknown Origin
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**Case**: A 34 year old female with Hashimoto's thyroiditis and IBS was admitted to neurosurgery with complaint of two weeks of vision change (bilateral hemianopia) and headache. MRI revealed diffuse homogeneously enhancing lesion involving the pituitary gland, pituitary stalk, and hypothalamus, measuring approximately 1.7 x 1.8 x 2.2 cm. Labs on admit: FSH 1.9 mIU/ml, LH <0.1 mIU/ml, PRL 42.7 ng/ml (ref range 5.2-26.5), TSH 0.01 uIU/ml (ref range 0.4-4), free T4 0.85 ng/dl (0.71-1.51), random cortisol 2.4 ug/dl, HgbA1C 5.6% (ref range 4.5-6.2%). Biopsy was performed and the pathology was consistent with granulomatous hypophysitis. Post operatively, patient developed diabetes insipidus and was started on DDAVP. Other pathologies were ruled out with negative interferon gold TB, non reactive RPR, ACE 33 U/l (ref range 8-53), c-ANCA and p-ANCA both <1:20 (normal <1:20), rheumatoid factor <10 IU/ml (ref range 0-15), MPO 2 U (normal <20), and a CT scan which revealed no peripheral granulomas. Despite being prescribed prednisone, patient continued to have worsening symptoms of headache, visual disturbance and fatigue over the course of three months. Repeat MRI revealed persistent enhancement associated with an infiltrative process invading the pituitary gland, optic chiasms, and optic tracts. Patient underwent an endonasal transsphenoidal resection of the pituitary gland. Pathology again revealed granulomatous hypophysitis. Post op labs showed: FSH 0.6 mIU/ml, LH <0.1 mIU/ml, PRL 2.3 ng/ml (ref range 5.2-26.5), TSH <0.010 uIU/ml (ref range 0.4-4), free T4 1.02 ng/dl (0.71-1.51). Six months later, patient continued with symptoms of headaches and central scotoma. MRI revealed increased globular enhancement within the sella with slight expansion with suprasellar extension involving the hypothalamus with chiasmal compression. Patient is scheduled for repeat surgery on 1/16/2017.  **Conclusion**: Granulomatous hypophysitis is a rare and life threatening disease. We present a case of a patient with recurring granulomatous hypophysitis despite surgical intervention.

The authors have no relevant relationships to disclose.

P60
An Unusual Case of Neurocytoma Presenting as Hypothermia with Hypothalamic Syndrome and Panhypopituitarism
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**Background**: The vast majority of brain lesions that interfere with pituitary function arise in the sella; however, tumors that originate from other structures of the brain may also invade the hypothalamic-pituitary space and give rise to panhypopituitarism. Here we describe an unusual case of very rare malignant neoplasm atypical neurocytoma, which comprise 0.1-0.5% of primary brain tumors which invaded the sellar region and resulted in hypothalamic dysfunction causing hypothermia as well as panhypopituitarism. **Case**: A 65 year old male with no significant past medical history developed hypothermia with a rectal basal body temperature of temp 93 degrees which was incidentally noted during his urgent care visit for transient slurred speech. MRI revealed a lobulated, heterogeneously enhancing mass 2.6 cm X 1.7 cm X 3.0 cm in size in the sellar region extending into the intraventricular space causing obstructive hydrocephalus. Patient denied headache or visual disturbances. On presentation his lab work showed panhypopituitarism, with a TSH was 0.16 uIU/ml, free T4 0.59 ng/dl, serum cortisol 1.30 ug/dl, ACTH <5 pg/ml, testosterone 6 ng/dL. He was started on dexamethasone to reduce brain edema, as well as levotyroxine replacement. The patient underwent transcranial surgical resection of the mass; pathology showed a rare atypical neurocytoma. Patient received post-operative radiotherapy with gamma knife. Patient’s post op course was complicated by diabetes insipidus, hypothalamic dysregulation including hypothermia, bradycardia, polyphagia, rapid weight gain, sleep disturbances, emotional disturbances. **Conclusion**: Atypical central neurocytomas can rarely invade the sellar area. When hypothalamic dysfunction is present with panhypopituitarism, a wide differential diagnosis should be considered.

The authors have no relevant relationships to disclose.
P61
Changes of GH Axis After Transsphenoidal Adenomectomy in 1766 Patients with Pituitary Adenoma
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Objective: Although surgery itself could induce the GH deficiencies (GHD), changes of pituitary hormones and removal of mass effect after TSA might influence on the secretory function of GH axis. In this study, we evaluated the changes of GH axis in patients with pituitary adenoma (PA) after transsphenoidal adenomectomy (TSA).

Research Design and Methods: GH axis had been evaluated in patients with PA before and at least 2 times with 1.5 years intervals after TSA.

Results: Among 1766 enrolled patients, they were consisted of 536 (30.4%) in GH-secreting PA, 90 (5.1%) in Cushing disease, 255 (14.4%) in prolactinoma, 32 (1.8%) in TSH-secreting PA, and 853 (48.3%) in nonfunctioning PA (NFPA). The frequency of preoperative GHD was significantly higher in patients with Cushing disease (68/90; 75.6%) than subjects with prolactinoma, TSH-secreting PA, and NFPA (66/255; 25.9%, 6/32; 18.8%, and 511/853; 60.0%, respectively) (P < 0.001). After TSA, newly developed GH deficiencies were diagnosed in 49/534 (9.2%) in GH-secreting PA, 9/22 (40.9%) in Cushing disease, 17/189 (9.0%) in prolactinoma, 1/26 (3.8%) in TSH secreting PA, and 46/342 (13.5%) in NFPA. Among the patients with GHD before TSA, the recovery rates of GH axis were 25/68 (36.8%) in Cushing disease, 37/66 (56.1%) in prolactinoma, 4/6 (66.7%) in TSH-secreting PA, and 158/511 (30.9%) in NFPA. Younger age (42.22±12.49 vs. 48.05±12.95, P=0.014), female gender (135/338; 39.9% vs. 91/315; 28.9% P<0.001), and low grade Hardy classification (31/60; 51.7% vs. 42/67; 62.7%, 122/409; 29.8% vs. 31/117; 26.5%, Hardy I, II, III, and IV, respectively, P<0.001) were significantly associated with recovery of GH axis from GHD after TSA.

Conclusions: The changes of GH axis after TSA were different according the classification of PA. These data provide the first clinical evidence that differentiated evaluations for GHD should be applied according to the classification of PA.

The authors have no relevant relationships to disclose.

P62
Comparison of the Cortisol and GH Responses to Provocative Testing with Glucagon and Insulin Hypoglycemia in Pituitary Disease
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Background: Assessment of the hypothalamic–pituitary–adrenal and somatotropic axes integrity in pituitary diseases is crucial. The insulin tolerance test (ITT) has been used as gold standard to assess the adequacy of both axes. Nevertheless, it is contra-indicated in some patients due to potential adverse effects. In this scenario, the glucagon stimulation test (GST) emerges as a useful alternative test.

Objective: To compare cortisol and GH responses to glucagon (1 mg IM) and to insulin (0.1-0.2 U/kg IV) in patients harboring pituitary disease.

Methods: Twenty patients (9 acromegals, 6 with non-functioning pituitary tumors and 1 with medulloblastoma submitted to radiotherapy) were included. Glucose, cortisol and GH levels were measured at 0, 30, 60, 90, 120 and 180 min during GST and at 0, 15, 30, 45, 60 and 90 min during the ITT. The results were analyzed by median and a ROC curve was built to identify the best cut-off for basal cortisol and for cortisol and GH peaks in GST compared to ITT, in order to detect patients with hypocortisolism and GH deficiency (GHD). During ITT, a cortisol peak < 18 µg/dL and GH < 3 ng/mL were used as the cut-off for hypocortisolism and GHD respectively. Results: The mean age was 49 (18-74) years and mean BMI was 29 (24-44) kg/m2. For hypocortisolism assessment, the best basal cortisol cut-off was 8.5 µg/dL (85.5% sensitivity and 92.3% specificity - p=0.09) while the cortisol peak in the GST was 18 µg/dL (71.4% sensitivity and 84.6% specificity – p=0.036). For diagnosis of GHD the best GH peak cut-off in the GST was 1.75 (100% sensitivity and specificity – p=0.01).

Conclusion: Compared to literature data, GST cortisol peak cut-off for hypocortisolism diagnosis was in agreement and GH peak cut-off for GHD revealed a lower level as already suggested by other groups.

The authors have no relevant relationships to disclose.
P63
Declining FT4 Concentrations Following High Dose Cranial Irradiation: Sign of Early Development of Central Hypothyroidism?

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Background: GH secreting cells have been reported to be more vulnerable to cranial radiotherapy (cRT) compared to TSH secreting cells. Declining FT4 concentrations prior to GH deficiency (GHD) in irradiated childhood brain tumor survivors (CBTS), may however indicate simultaneous radiation damage to TSH secreting cells. Our aim was to validate the clinical observation of declining FT4 concentrations in irradiated CBTS in a nationwide cohort prior to or shortly after the diagnosis GHD. Methods: A nationwide cohort study included children who developed GHD, after cRT for a brain tumor diagnosed in the period 2002 and 2012, and surviving >2 years after diagnosis. CBTS with primary hypothyroidism were excluded. Results: Sixty-one CBTS were included with a median follow-up time of 8.6yr (range 2.5-13.3) after tumor diagnosis. All CBTS had a normal pituitary function at tumor diagnosis. The total median cRT dose was 54Gy (range 15-72Gy). Eleven of 61 CBTS (18.0%) were diagnosed with central hypothyroidism (CeH) prior to the diagnosis of GHD. In the other 50 CBTS (82.0%), mean FT4 concentrations declined from 15.7 pmol/l at start of tumor treatment to 14.2 pmol/l (p<0.01, CI 0.74-2.20) at diagnosis of GHD. Forty-five of 50 CBTS started on GH treatment after starting GH treatment, a further decline of mean FT4 concentration was seen (11.7 pmol/L (p<0.01, CI 1.20-3.52). In 25 of these 45 CBTS, T4 free patients were diagnosed as congenital pituitary hormone deficiencies at the first admission to the hospital, but other patients were diagnosed during follow-up. Serum aminotransferase levels were very high in two patients and only moderately elevated in the others. Combined adrenal, thyroid, and growth hormone deficiencies were diagnosed in two patients. The other patients had various combinations of adrenal, thyroid, and growth hormone deficiencies. Remission of cholestasis was between 10 days to 2 months after hormone replacement was started. Conclusion: The observation that in 18.0% of CBTS treated with cRT, CeH has been diagnosed before diagnosing GHD and that mean FT4 concentrations decline in the remaining 82.0% prior to the diagnosis GHD, may indicate that CeH occurs earlier than currently suspected.

H.N. Caron is an employee of Roche. The other authors have no relevant relationships to disclose.

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Hyperbilirubinemia and Cholestasis Due to Congenital Hypopituitarism

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Background: Cholestatic jaundice in early infancy is a complex diagnostic challenge. Cholestasis due to endocrine diseases is not common and poorly recognized. Patients and Methods: Six patients were included in the study followed-up by Departments of Pediatric Gastroenterology, Hepatology and Nutrition and Pediatric Endocrinology at the University Hospital. Results: The median age at admission of the patients was 2.5 months. Three patients were diagnosed as congenital pituitary hormone deficiencies at the first admission to the hospital, but other patients were diagnosed during follow-up. Serum aminotransferase levels were very high in two patients and only moderately elevated in the others. Combined adrenal, thyroid, and growth hormone deficiencies were diagnosed in two patients. The other patients had various combinations of adrenal, thyroid, and growth hormone deficiencies. Remission of cholestasis was between 10 days to 2 months after hormone replacement was started. Conclusion: Hypopituitarism should be considered in the differential diagnosis of hyperbilirubinemia in infants. It is possible to prevent complications secondary to cholestasis and mental retardation if hypothyroidism and other pituitary hormone deficiencies are treated as soon as possible. Early diagnosis of cholestasis due to hormonal deficiencies is crucial to avoid poor prognosis.

The authors have no relevant relationships to disclose.
Implied Work Productivity in Patients with Pituitary Tumors – A Cross-sectional Study

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Introduction: Chronic pituitary conditions often develop in patients under 65 years old and thereby may, apart from clinical symptoms, have a significant impact on patients’ ability to work. Research on the occurrence and extent of work disability in patients with chronic pituitary conditions however is scarce. Objective: To investigate long-term effects on work status in patients treated for pituitary adenomas. Methods: All patients diagnosed with a pituitary condition, previously treated in the Leiden University Medical Center, still in clinical follow-up, and aged 18-65 years old were eligible for this study. They were approached by regular mail to complete a set of questionnaires on work status including the validated Short Form-Health and Labour Questionnaire (SF-HLQ) and the Work Role Functioning Questionnaire (WRFQ 2.0), the latter given to patients with a paid job, and indicates health-related work functioning (work scheduling/output demands, physical demands, mental/social demands and flexibility demands). Quality of life was assessed with the Leiden Bother and Needs Questionnaire (LBNQ) and the Short Form-36 (SF-36). Multiple regression analysis will be performed, looking specifically at individual tumor types and follow-up duration. Results: To date a total of 266 patients (of estimated 500) have been included. Mean age is 50.1 (±10.4) years and mean follow up 13.2 (±10.8) years. In total 44% of all patients have a paid job, of these 40% reported missing work due to health related problems in the last year. The overall WRFQ-score, shows a mean score of 68.9 (±17), compared to normative data of healthy controls 84.2 (±15.8). Discussion: A very high percentage of pituitary patients are without a paid job and those with a job show on average a clinically relevant impairment at work. Further prospective studies are necessary to assess determinants that can be used as a foundation for our interventional/prognostic studies in the near future.

The authors have no relevant relationships to disclose.

Isolated Thyrotropin (TSH) Deficiency During Primary First-generation Somatostatin Analog (SMSa) Treatment in Patients with TSH-secreting Pituitary Adenomas

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The standard treatment of TSH-secreting pituitary adenoma is transphenoidal or endoscopic pituitary adenomectomy. Due to the presence of somatostatin receptor subtypes (sst2-5) on adenomatous cells, first-generation SMSas (octreotide, lanreotide) may serve as an alternative therapeutic approach in some patients. Isolated TSH deficiency has rarely been reported during primary SMSa treatment of such patients.

We describe hormonal and radiological data of five women (31 to 54 years old) with TSH-secreting adenoma (microadenoma : n = 1; macroadenoma : n = 4), primarily treated with long-acting SMSas (sandostatine LAR n = 3, somatuline Autogel n = 2), with occurrence of an isolated TSH deficiency. In 3 patients, it appeared after the first injection (12 to 30 days), for 1 patient after the second one (60 days). For those 4 patients, concentrations of TSH decreased from 9.2 ± 8.3 mUI/L to 0.27 ± 0.23 mUI/L, FT4 from 35.8 ± 8.3 pmol/l to 10.1 ± 1.5 pmol/l and FT3 from 14.1 ± 3.8 pmol/l to 2.5 ± 0.9 pmol/l. In 2 patients, pituitary MRI revealed a rapid shrinkage of adenoma volume. The fifth patient presented a mixed TSH/GH macroadenoma, and isolated central hypothyroidism appeared during long-term sandostatine LAR treatment (20 mg/month), when the dose was increased in order to control GH/IGF-1 hypersecretion: TSH level decreased from 5 mUI/L to 3.8 mUI/L, FT4 level from 31 to 10.6 pmol/l and FT3 level from 13.1 to 3.2 pmol/l.

In conclusion, in patients with TSH-secreting pituitary adenomas isolated TSH deficiency can be observed during primary SMSa treatment. Its early occurrence seems to be a predictive factor for hormonal and tumor response to SMSa treatment, and its presence may require to reduce SMSa dosage or to introduce substitutive treatment with levothyroxine.

The authors have no relevant relationships to disclose.
Low Dose of Imatinib Mesylate Causes GH Reduction In Cultured Somatotropinoma Cells

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Introduction: Acromegaly is a neuroendocrine disorder caused by excessive secretion of growth hormone (GH). Current treatment includes surgery, radiotherapy and drugs like somatostatin or dopamine receptor agonist. In spite of combination of therapies cure rate is dismal. There is a quest for new therapeutic targets with optimal efficacy, least side effect with low cost in resource constraint countries. Tyrosine kinase inhibitor (Imatinib) has been shown to cause growth failure in pediatric chronic myeloid leukemia (CML) cases by targeting the GH/IGF-1 axis. There is no study to report the effect of TKI on somatotropinoma either in vitro or in vivo. Here we present data on the effect of Imatinib on GH release from primary cultures of human somatotropinomas and GH3 cell line.

Material and Method: Differential expression of imatinib target (c-kit, VEGF, PDGFR-α and β) was studied on 157 pituitary adenoma samples. The results were confirmed using western blot and RT-PCR. Both GH3 cell line and primary culture of somatotropinomas (n=20) were cultured and treated with graded concentration of imatinib mesylate. The drug effects were studied using GH assay, cell viability assay, immunocytochemistry, electron microscopy and apoptosis analysis. The mechanism of action of imatinib was studied using human proteome profiling kit and bioinformatically by Consensus PathDB and String DB. Results: Somatotropinomas showed significantly higher cytoplasmic positivity for c-kit, PDGFR-β and VEGF to NFPA (P<0.009, P<0.001 and P<0.003, respectively). A low concentration (0.5µM) of imatinib showed maximum inhibition of GH secretion and increasing the dose did not impart any advantage to the inhibition. Imatinib inhibits GH secretion in both primary culture (P<0.01) and GH3 cell line (P<0.001). However, imatinib treatment does not affect cell viability (P<0.88) and apoptosis (P<0.06). The receptor tyrosine kinase array and bioinformatics analysis showed there is a crosstalk between GHR and PDGFR-β. Imatinib inhibits GH signaling via PDGFR-β/ PKC pathway.

Conclusion: Imatinib inhibits GH secretion in somatotropinoma cells without affecting cell viability. This may open a new vista for management of somatotropinomas.

The authors have no relevant relationships to disclose.

Low Grade Pneumatization of Sphenoid Sinus is No Longer a Contraindication to Transsphenoidal Surgery: A Retrospective Study

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Background: The transsphenoidal approach (TNS) is considered the gold standard for resection of pituitary adenomas and other sellar region lesions. This approach is guided by few fundamental anatomical landmarks that guide the surgeon toward the sellar floor. Some anatomical structures may vary a lot (e.g. intrasphenoidal septa, intercarotid distance) or are not always easy to find. Among those, the pneumatization and conformation of the sphenoidal sinus (SS) plays a key role for accessing the floor of the sella and other skull base structures. In fact, a poorly pneumatized SS may be a relative contraindication to the TNS approach requiring a transcranial approach which is associated with a higher complication rate. Materials and methods: A consecutive series of 243 patients submitted to TNS approach for sellar lesion was analyzed. Patients with a poor pneumatization of the SS were included. Neurosurgical and endocrinological outcomes were reported. Results: 15 patients with a low grade pneumatization of the SS were successfully treated using a TNS approach matched with neuronavigation and Doppler US. 13/15 had a pituitary adenoma. Endocrinological and neurosurgical outcome were also similar to patients with normal pneumatization of the SS showing a cured disease in 7/9 patients with functioning adenomas and an improvement of symptoms in case of non functioning adenomas. Conclusions: TNS surgery for sellar lesions offers low complication rates and good clinical outcome. Patients with a poorly pneumatized SS can be treated safely with a TNS approach using image guidance techniques in order to avoid major neurovascular complications.

The authors have no relevant relationships to disclose.
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Normal Quality of Life (QoL) in Non-radiated Panhypopituitary Patients on No Growth Hormone (GH) Replacement Treated with Contemporary Glucocorticoid Doses

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Objectives: AGHD (adult growth hormone deficiency) was shown to be associated with lower QoL vs controls. However, effects of age, supraphysiologic doses of hydrocortisone, radiation therapy and sinonasal sequelae of surgery were never taken into account. We compared hypopituitary patients with AGHD after surgery alone (N=34) and surgery + XRT (N=17) with controls (N=43) who had sinonasal surgery for benign disease, recruited from pituitary and otolaryngology clinics, respectively. Growth hormone deficiency was defined as presence of at least 3 additional hormone deficiencies with low IGF-1 and/or GH <1.0 ng/ml during insulin tolerance test. Replacement with hydrocortisone, testosterone (in men), DDAVP and thyroxine was given. No estrogen was given in women. Mean hydrocortisone dose was 14.2+/-.9 mg/day. No patient had ever been treated with GH. Methods: We administered disease-specific, QoL-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) and benign sinus disease specific, Sino-Nasal Outcome Test (SNOT-22) questionnaires in each group. Higher scores suggest poor QoL on both surveys. Data was analyzed by Student’s t-test and expressed as mean +/- SEM. P < 0.05 was considered significant. Study was approved by institutional review board. Results: Controls were slightly younger than hypopituitary patients (57.3+/1.3 vs 61.6+/1.8 years, p=0.03). Plasma IGF-1 in patients was pathologically low at 83+/7 ng.ml. In the entire group, AGHDA score was worse than in controls (7.7+/-.9 vs. 5.2+/-.1, p=0.04). However, this difference disappeared when controls and non-radiated patients were compared (5.2+/-.10 vs 6.6+/-.12, p=0.4), and entire difference was driven by radiated group (9.9+/-.6, p=0.01). SNOT-22 scores did not differ between controls and patients as a whole (16.4+/-.2 vs. 21+/-.2, p=0.15). Conclusion: We conclude that when compared with controls of their own age group, patients with AGHD treated with contemporary doses of glucocorticoids but having no history of cranial radiation have normal quality of life despite absent GH replacement.

The authors have no relevant relationships to disclose.

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Open for Discussion: How to Proceed Towards a Value Based Health Care Integrated Practice Unit for Pituitary Adenoma Patients

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Background: The outcome of patients with pituitary tumors is highly variable, but on average long-term mortality is increased, and physical and psychosocial impairments persist despite state of the art treatment. Unfortunately, literature data have limitations in providing prognostic data for decision making today, because of the small size and heterogeneity of patients, combined exposures, lack of randomized studies, and ongoing innovations in pituitary care. The value base health care (VBHC) principle by Porter evaluates care as delivered today and added value of treatments. We describe our ongoing efforts to improve care of pituitary disease at maximal added value/ optimal cost to open the discussion how to shape future pituitary care. Approach: The long-term clinical outcome data of our center have been extensively evaluated since the start of dedicated transsphenoidal surgery from the late 1970s, including data on mortality, morbidity, quality of life, patients’ perception, bother and needs. Today’s patients’ expectations and social outcome are currently being evaluated. Our pituitary practice was extensively discussed and adjusted accordingly using previous data, literature evidence and expert opinion. Identified processes of special interest were referral and planning of first visit, perioperative care, and evaluating the need for chronic care. Patient centred care was detailed for all health care providers with task description and proposed outcome parameters. The following adjustments were made: first visit; personalized intake, weekly multidisciplinary clinic and team meetings; perioperative period; pre- and post-operative multidisciplinary counselling to fine-tune patient management; improved surgical decision making through team surgery; increased self-care in early discharge if uncomplicated procedure; chronic care: use of bother and need questionnaire, self management education program. Monthly evaluation of the process and patient outcomes (PDCA cycle) are anticipated. The ultimate aim is to provide short time evidence for improved patient outcomes and patient satisfaction, at a time- and cost-efficient fashion.

The authors have no relevant relationships to disclose.
Pre-Surgical Peak GH Levels During GH Releasing Peptide (GHRP)-2 Test Sensitively Reflect The Severity of Hypopituitarism in Non-Functioning Pituitary Adenoma (NFPA)

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Objective: NFPA is one of the most common causes of hypopituitarism in adulthood. In this study, we investigated factors that predict the severity of hypopituitarism in patients with NFPA. Patients and Methods: Fifty patients who underwent transsphenoidal surgery for NFPA (M 26/F 24, age 60±14 years) were studied. Severity of hypopituitarism was evaluated by preoperative basal hormone levels and results of dynamic tests. GH secretory status was evaluated by GHRP-2 test. Patients were classified into three groups according to the severity of hypopituitarism as follows; normal group (gr. N), mild group (gr. M: 1 or 2 axis deficiency) and severe group (gr. S: 3 or 4 axis deficiency). Clinical manifestation, age, sex, BMI, tumor size and extension and the peak value of GH undertaking GHRP-2 test before surgery were investigated and compared among three groups. Results: There were no significant differences among gr. N (n=16), gr. M (n=23) and gr. S (n=11) in clinical manifestation, age, sex and BMI. Degrees of tumor extension evaluated by MRI findings did not predict the severity of hypopituitarism, though hyperprolactinemia was most frequent in gr. S (gr. N: 25%, M: 25% and S: 55%). Pre-surgical peak GH levels during GHRP-2 test were 26.7±16.5 ng/ml in gr. N, 8.9±7.1 ng/ml in gr. M and 1.8±1.1 ng/ml in gr. S. Conclusion: Among various factors studied, pre-surgical peak GH levels during GHRP-2 test reflected the severity of hypopituitarism most sensitively.

The authors have no relevant relationships to disclose.

The Investigation of Anti-TPIT Antibodies in Adult-Onset Isolated ACTH Deficiency

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Background: It is known that PIT-1 gene mutations are responsible for congenital GH, PRL, and TSH deficiency, and 65% cases of congenital complete isolated ACTH deficiency (IAD) are caused by TPIT mutation (J Clin Endocrinol Metab. 2012;97:E486). Recently, “anti-PIT-1 antibody syndrome” characterized by adult-onset GH, PRL, and TSH deficiencies and existence of anti-PIT-1 antibodies in patients’ sera was reported as a new type of autoimmune polyendocrine syndromes (APS). The endocrinological character is common between neonatal and adult onset of GH, PRL, and TSH deficiencies. Since we considered that autoimmunity against TPIT protein might be responsible for adult-onset IAD in a similar way to the “anti- PIT-1 antibody syndrome”, we investigated autoantibodies against TPIT, which is POMC specific transcriptional factor, in sera of adult-onset IAD patients. Patients and Methods: We examined five cases of adult-onset IAD (female 54 y/o, male 72 y/o, male 62 y/o, male 54 y/o, female 38 y/o). Immunoblotting analysis of patients’ sera using HEK293T cells (TPIT overexpression cells) lysates was performed. Result: We could not detect the anti-TPIT antibodies in sera of five cases of adult-onset IAD. Conclusions: We could not demonstrate new etiology of five cases of adult-onset IAD. Both adult-onset IAD and “anti-PIT-1 antibody syndrome” are known to accompany with other autoimmune disease. Since there still remains a possibility of anti-TPIT antibodies associating with adult-onset IAD, further study is needed.

The authors have no relevant relationships to disclose.
**PROLACTININ/PROLACTINOMA**

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**Combination Therapy of Bromocriptine and Metformin in Refractory Prolactinomas**

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**Purpose:** Refractory prolactinomas are recently proposed to define invasive-aggressive tumors with high Ki-67 indexes, exhibit aggressive behaviors, early and frequent recurrence, and resistance to dopamine agonists, surgery, radiotherapy. Recently, metformin has been proposed as a cancer treatment. The purpose of this study was to summarize the results of 2 patients with refractory prolactinoma treated with combination of bromocriptine and metformin and its underlying mechanisms involved. **Methods:** Retrospective review of data of 2 patients with refractory prolactinoma treated with combination of bromocriptine and metformin extracted from clinical files. AMPK signal pathways in human prolactinomas tissues in bromocriptine sensitive and resistant groups were analyzed. After activation of AMPK signal pathways by AICAR or metformin, prolactinomas related receptors such as ER\(^\alpha\), ER\(^\beta\) and D2R expression variation and tumor cell proliferation and apoptosis were analyzed. The MMQ and GH3 xenograft tumor models were used to verify the results in cell experiments. **Results:** Bromocriptine, combined with metformin in the 2 patients with refractory prolactinomas resulted in decreased PRL levels and tumor size. D2R receptors expression was significantly decreased in bromocriptine resistant group. AICAR and metformin could downregulate the expression of ER\(^\alpha\) and ER\(^\beta\) and thereby inhibit the tumor proliferation and promote apoptosis, and slightly upregulate the D2R expression. In combination with metformin, bromocriptine can distinctly inhibit the tumor growth and PRL levels of animal xenograft models. **Conclusions:** Bromocriptine combined with metformin might be a novel treatment for the refractory prolactinomas. Activation of AMPK signal pathway could downregulate the ER expression to inhibit the tumor proliferation, prompt the apoptosis and upregulate the D2R expression, which could be the underlying mechanisms involved.

The authors have no relevant relationships to disclose.

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**P70**

**Extreme Hyperprolactinemia in the Absence of a Macroprolactinoma**

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**Introduction:** Hyperprolactinemia is a common endocrine condition caused by a variety of conditions. The most common causes are medication induced, pituitary tumors and systemic disease such as hypothyroidism, liver and renal failure. The degree of elevation generally correlate with the etiology, and in the case of pituitary tumors, it parallels the tumor size, with levels >500 ng/dl considered diagnostic of macroprolactinoma. **Clinical case:** We report a 35-year-old male with medical history of ESRD, sickle cell thalassemia complicated by iron overload, hypertension and seizure disorder, admitted to the hospital with severe right-sided chest pain. The patient also reported significant fatigue, impotence, decreased libido and galactorrhea for the last 3 months. Before admission, he was taking oral opiates for chest pain without response. His other medications included valsartan, labetalol, amlodipine and carbamazepine. Laboratory tests showed a serum prolactin level of 2056 ng/ml, confirmed on repeated measurements, artifacts excluded. Pituitary function tests, including thyroid, ACTH, cortisol and IGF-1, were within normal range, LH was <1.1 mIU/mL, FSH of 4.8 mIU/mL and total testosterone of 12 ng/dL. MRI of brain without contrast showed no evidence of pituitary adenoma or obvious pituitary or other brain abnormalities. Treatment with daily bromocriptine 2.5 mg resulted in a rapid decline of prolactin to 1363 ng/dl after 3 days. **Discussion:** This is a rare case of extreme prolactin elevation, in the absence of a pituitary macroadenoma. The etiology was likely multifactorial with contribution of renal failure, medication side effect from opiates, neurogenic stimulation from chest pain, and possibly pituitary pathology, a microprolactinoma. As this will affect diagnostic and therapeutic approach, it is important to recognize that very high prolactin levels can occur in the absence of large pituitary tumors as a result of multiple etiologies.

The authors have no relevant relationships to disclose.
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Pituitary Tumor Suppression by Combination of Cabergoline and Chloroquine

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Context: Dopamine agonist cabergoline (CAB) has been used widely in treatment of prolactinomas and other types of pituitary adenomas; but its clinical use is hampered by intolerance in some prolactinoma patients and lack of effectiveness in other pituitary tumor types. Chloroquine (CQ) is an old drug widely used in treatment of malaria. Recently studies, including our own, revealed that both CAB and CQ are involved in induction of autophagy and activation of autophagic cell death. Objective: We want to test whether CAB and CQ may function cooperatively in suppression of pituitary adenomas as well as other cancers. Methods: Evaluation of CQ with CAB in cell death was assessed by cell proliferation assays, flow cytometry, caspase activity assays, xenograft animals and rat prolactinoma model. Animals were sacrificed by anesthesia and were autopsied. Interpretation of this treatment was by confocal immunocytochemistry, inhibitors and RNA interference.

Results: In vitro studies using rat pituitary tumor cell lines MMQ and GH3, human pituitary tumor cell primary cultures, and several human cancer cell lines showed that combination of CAB and CQ enhanced suppression of cell proliferation by CAB alone; and these results were confirmed in in vivo models of xenograft nude mouse and estrogen-induced rat prolactinoma. To understand the mechanism of combined CAB and CQ action, we established a low CAB dose condition in which CAB was able to induce autophagy but failed to suppress cell growth. Addition of CQ to the low dose CAB blocked the normal autophagic cycles and induced apoptosis, which was evidenced as the further accumulation of p62/caspase-8/LC3-II. Conclusion: Our data suggests that combined use of CAB and CQ may increase clinical effectiveness in treatment of human pituitary adenomas as well as other cancers, making it an attractive option in tumor and cancer therapies.

The authors have no relevant relationships to disclose.

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Prolactinoma in Children and Very Young Patients: A Single Center Experience

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Background: Prolactin secreting tumors account for 50–70% of all pituitary adenomas in children. Most of them are macroadenomas and first-line therapy with dopamine agonist results in prolactin normalization and tumor shrinkage in 80% of patients. Methods: We retrospectively analyzed a series of 31 children and young patients with prolactinomas that were diagnosed between 1986 – 2015. 25 were female (80%) and 6 were male (20%). Mean age at diagnosis was 16.5 +/- 2.5 (9–24y). In all cases MRI showed a pituitary macroadenoma and 27 patients (87%) suprasellar and/or parasellar extension was observed. The initial prolactin blood level ranged between 119 and 27,640 ng/mL. Results: The most important clinical manifestations were amenorrhea (80%), puberal delay (52%), visual abnormalities (48%), headache (32%), galactorrhea (29%), growth retardation (16%) and weight gain (23%). In 5 cases, patients were referred with a misdiagnosis of other suprasellar tumors and prolactinomas were truly assessed measuring tumoral prolactin levels. In patients with strict follow-up 27/31 (87%) showed normalization of prolactin and tumor volume reduction after medical treatment with a dopamine agonist. Conclusion: Prolactinomas in children and young patients occurs mainly in girls and most of them are macroadenomas. Amenorrhea was present in the majority of female patients; headaches and visual impairment were the first symptoms in male. Treatment with dopamine agonist resulted in prolactin normalization and tumor shrinkage in 87% of patients, being cabergoline better tolerated than bromocriptine. Reduction in prolactin levels into normal range was accompanied with restoration of visual fields and in some cases complete disappearance of the adenoma. Surgical tumor removal was not curative in patients when this procedure was performed. Children with prolactinomas respond to dopamine agonist and must be properly evaluated to avoid unnecessary therapeutic modalities.

The authors have no relevant relationships to disclose.
Surgical Outcomes & Complications of Endoscopic or Microscopic Transsphenoidal Resection of Prolactinomas in a Pituitary Center

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Introduction: Surgical resection (TSSR) of prolactin-secreting adenomas is usually reserved for those who are intolerant or resistant to dopamine agonist (DA) therapy. Data regarding predictors of persistent disease after surgical resection is sparse. Methods: A retrospective chart review of patients undergoing TSSR for prolactinoma at Keck Medical Center was conducted from 1995 to 2016. Data was retrieved from the USC Pituitary Tumor Registry, which includes more than 1700 patients. Data was verified by chart analysis. All patients received a pre-operative workup and MR imaging to determine the size of adenoma and extent of invasion. Diagnosis of prolactinoma was based on clinical presentation and confirmed by histopathology of surgical specimens. Hormonal remission was defined as normalization of prolactin levels. Patients were grouped by hormonal remission vs. non-remission and analyzed by two-tailed Fisher’s exact test or an unpaired t-test (p<0.05). Results: 47 cases were included. The majority of cases was female (74.5%). Average age at the time of surgery was 36.5 years. Invasive tumors were found in 74.5% of patients. Gross total resection was achieved in 66%. Hormonal remission was achieved in 51%. Of those that achieved hormonal remission; 15 did so without additional medications and 9 with post-surgical DA therapy. Hormonal non-remission group (n=23) had significantly higher preoperative prolactin levels than the hormonal remission group (n=24) (mean=619.2ng/ml vs 230.8 ng/ml, p=0.034). Tumor invasion was associated with post-operative hormonal non-remission (p=0.017). Gender, age, tumor diameter, and gross total resection were not significant predictors of hormonal remission. Conclusion: Preoperative prolactin levels and presence of invasion, particularly into the cavernous sinus may predict disease persistence after resection. Although prolactinomas are more common in females, gender did not appear to not play a role in predicting hormonal remission.

The authors have no relevant relationships to disclose.

Results of Biopsy-Proven Germ Cell Tumors in Neurohypophyseal-Suprasellar Regions: Nine Years’ Experience in a Single Center

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Background: The biopsy is recognized as the most accurate method to determine the histological characterization of germ cell tumors in neurohypophyseal-suprasellar (nsGCT) regions. It is very difficult to evaluate the prognosis before histological confirmation. Objectives: This study aimed to evaluate the independent prognostic risk factors of patients with germ cell tumors (GCTs) in neurohypophyseal-suprasellar regions. Methods: From January 2008 to December 2015, 61 patients who were histologically diagnosed as GCTs in neurohypophyseal-suprasellar regions did follow-ups and were included in this retrospective study. Results: Of 61 patients in this study, 40 (65.6%), 10 (16.4%), 11 (18.0%) were diagnosed as pure germinomas, germinomas with syncytiotrophoblastic giant cells (STGC) and non-germinomatous germ-cell tumors (NGGCT), respectively. The patients with pure germinomas had a significantly better overall survival time than those with NGGCT (56.47 ± 3.01 months vs 43.09 ± 10.58 months, p = 0.01). Multivariate analysis demonstrated the independent poor prognostic risk factors of patients with GCTs in neurohypophyseal-suprasellar regions were the most diameters more than 15mm (OR 7.40; 95% CI 2.01-27.19), OCT positive (OR 5.97; 95% CI 1.40-25.48) and NGGCT (OR 11.88; 95% CI 2.37-59.50), while the combination of chemotherapy and radiotherapy (RT) was associated with a better prognosis (OR 0.15; 95% CI 0.04-0.55). Conclusions: The most diameters more than 15mm, OCT positive or NGGCT, was associated with a poorer prognosis for patients with GCTs in neurohypophyseal-suprasellar regions, while the combination of chemotherapy and RT was associated with a better prognosis.

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