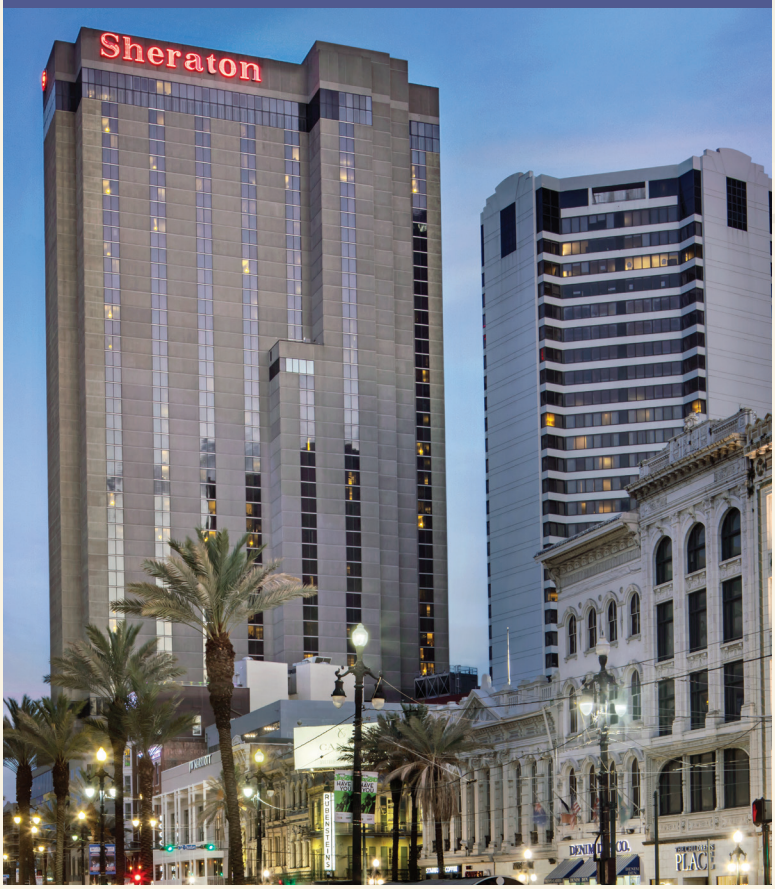
The Pituitary Society

presents the

16th SIXTEENTH INTERNATIONAL PITUITARY CONGRESS

MARCH 20 - 22, 2019

New Orleans, Louisiana



PROGRAM AND ABSTRACTS

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Welcome,

The Sixteenth 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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PITUITARY MASTER COURSE

Essentials of Pituitary Diseases for Fellows-in-Training

WEDNESDAY, MARCH 20, 2019		
9:30 a.m.	Getting to Know You	
10:30	Discussion of Course Objectives and Review of Participants' Feedback on Pre-Course Survey	*Maria Fleseriu, Christian Strasburger Course Co-Chairs*
Hypopituitarism		
10:45	Hypopituitarism: Guidelines versus Real-life Experience	*John Wass*
11:10	Updates in Diagnosis of Growth Hormone Deficiency	*Roberto Salvatori*
11:35	Outcomes in Treatment with Growth Hormone Replacement Therapy	*Shlomo Melmed*
12:00 Noon	Interactions Between Pituitary Hormonal Replacement Therapies	*Niki Karavitaki*
12:25 p.m.	Challenges in the Diagnosis and Management of Central Diabetes Insipidus	*Dana Erickson*
12:45	Cases by Participants and Faculty Panel Discussion	*John Carmichael, Fabienne Langlois*
1:15	Break	
Imaging of the Pituitary		
1:30	Case Based Discussion (working lunch)	*Mark Gurnell*
Updates in Hyperfunctioning Pituitary Tumors: Acromegaly; Cushing's Disease; and Prolactinomas		
2:00	How to Diagnose Acromegaly in Earlier Stages	*Sebastian Neggers*
2:25	Medical Therapy of Acromegaly: Mechanisms of Action, Stepwise Approach in Personalized Treatment	*Laurence Katznelson*
2:50	Diagnosis of Cushing's Disease, Initial Diagnosis and Recurrence	*Beverly MK Biller*
3:15	Medical Therapy of Cushing's Disease: Review of Available Options and Need for Individualized Treatment	*Maria Fleseriu*
3:40	Challenges in Prolactinomas Management	*Ann McCormack*
4:05	Cases by Participants and Faculty Panel Discussion	*Nienke Biermasz, Mônica Gadelha, Susan Samson*
4:35	Adjourn	

We gratefully acknowledge educational grants and other support for

The Pituitary Master Course – Essentials of Pituitary Disease for Fellows-in-Training

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SIXTEENTH INTERNATIONAL PITUITARY CONGRESS

WEDNESDAY, MARCH 20, 2019		
2:00 – 6:30 p.m.	Registration	
4:45 – 6:45 p.m.	Early Career Development Forum	
OPENING PLENARY DEBATE *Chairs: Julie Silverstein & John Wass*		
7:00 p.m.	WHO 2017 Classification of Pituitary Tumors – What is an Aggressive Pituitary Tumor?	*Beatriz Lopes, Ann McCormack, Gerald Raverot, Federico Roncaroli*
8:00 - 10:00	WELCOME RECEPTION	

THURSDAY, MARCH 21, 2019		
7:30 a.m.	Breakfast	
ACROMEGALY *Chairs: Annamaria Colao & Lisa Nachtigall*		
8:30	New Drug Classes for Treating Acromegaly	*Susan Samson*
8:50	Personalized Approach to Acromegaly Management: Precision Pituitary Medicine	*Manuel Puig-Domingo*
9:10	New Insights for Acromegaly: Prevalence, Presentation, Age and Gender	*Adriana Ioachimescu*
9:30	Where Are We for Combination Treatments?	*Sebastian Neggers*
9:50	Coffee Break & Poster Session	
TRANSLATIONAL SCIENCE *Chairs: Felipe Casanueva & David Clemmons*		
10:20	Functional Genomic Profiles of Pituitary Tumors	*Anat Ben-Shlomo*
10:40	Functional Effects of Pituitary Protein Sumoylation	*Eduardo Arzt*
11:00	Mechanisms for Immunotherapy-induced Pituitary Damage	*Yutaka Takahashi*
11:20	Immunotherapy and Pituitary Damage – Clinical Implications	*Alexander Faje*
MEET THE PROFESSOR (Select two sessions during registration)		
11:45 a.m. – 2:00 p.m.	Each session will be repeated one time	
	Diagnosis of Nonpituitary Sellar Masses: An Integrative Approach	*Luis Syro*
	Management of Drug-induced Hyperprolactinemia	*Philippe Chanson*
	Management of Residual Non-functional Adenomas After Surgery	*Yona Greenman*
	Perioperative Management of Cushing Disease	*Maria Fleseriu*
	Role of the "Bone Specialist" in the PTCOE	*Stefano Frara*
	The Challenge of Pseudo-Cushing's	*John Newell-Price*
HOT TOPICS *Chairs: Eliza Geer & Maria Chiara Zatelli*		
2:00	Reversibility of Impaired Brain Structures with Different Recovery Speeds in Short-term Cured Cushing's Disease: A Longitudinal Study Based on an Artificial Intelligence-assisted Tool	*Lu Gao*
2:15	Functional Human Hypothalamus-Pituitary Co-Organoid as a Novel Therapeutic Discovery Tool for Acquired Hypopituitarism	*Lorena Puto*

 Continued from page 4

2:30	Exploration of Novel Treatment for Cushing Disease	*Dongyun Zhang*
2:45	Safety of Once-weekly Somapacitan in Adult Growth Hormone Deficiency (AGHD): Data from a 53-week Open-labelled Extension of the REAL 1 Trial	*Gudmundur Johannsson*
3:00	Coffee Break & Poster Session	
GRS SYMPOSIUM *Chairs: Gudmundur Johannsson & John Kopchick*		
3:30	Criteria for Reestablishing the Diagnosis of GHD in Childhood Onset Patients During Transition and Assessment of Subsequent GH Responsiveness During Therapy	*Peter Clayton*
3:50	Tissue Specific Effects of GH Signaling	*Jens Otto Jørgensen*
4:10	Long-acting GH for Adults	*Andrew Hoffman*
4:30	The Continuum Between GH Deficiency and GH Insensitivity	*Vivian Hwa*
4:50	Poster Session	
5:30 – 6:30	CONGRESS RECEPTION	

FRIDAY, MARCH 22, 2019

7:00 AM	Continental Breakfast	
JOINT SESSION WITH NURSES & PATIENTS *Chairs: Anne Klibanski & Shlomo Melmed*		
8:00	Approval of Drugs for Orphan Diseases	*Peter Stein*
8:30	PANEL: Acromegaly Guidelines and Real-World Clinical Practice – Harmonization or Further Dichotomy	*Daphne Adelman, Laurence Katznelson, Karen JP Liebert, Jill Sisco*
9:10	Patient Reported Outcomes and Clinical Assessment Tools: Refinement of Acromegaly Treatment Goals	*Nienke Biermasz*
9:30	Coffee Break & Poster Session	
CRANIOPHARYNGIOMA *Chairs: Odelia Cooper & Niki Karavitaki*		
10:00	Genetics of Craniopharyngiomas	*Cynthia-Lillian Andoniadou*
10:20	Surgical and Radiosurgery Approaches	*Pietro Mortini*
10:40	Preserve or Sacrifice the Stalk? Endocrinological Outcomes, Extent of Resection and Recurrence Rates Following Endoscopic Endonasal Resection of Craniopharyngiomas	*Theodore Schwartz*
11:00	Oxytocin Effects in Craniopharyngioma Patients	*Hermann Müller*
CUSHING'S SYNDROME *Chairs: Anthony Heaney & Fahrettin Keleştemur*		
11:20	Epigenetics of POMC Regulation	*Jacques Drouin*
11:40	Advances in Cushing Disease Medical Therapies	*Beverly MK Biller*
12:00 Noon	Surgery for the Invisible Tumor in Cushing Disease	*Kalmon Post*
12:20 PM	Adrenal Stem Cells and Pathogenesis of Adrenal Cushing's Disease	*Gary Hammer*
CLOSING SESSION		
12:40	Presidential Address, Awards Presentation & Business Meeting	*Christian Strasburger*
1:00	CONGRESS ADJOURNS	
1:30	**SATELLITE SYMPOSIUM:** Acromegaly Management From the Physician and Patient Perspective	*Location: Rhythms 1 & 2*

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16th International Pituitary Congress

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OPENING PLENARY SESSION

Chairs: Julie Silverstein and John Wass

JS and JW have no relevant relationships to report.

WHO 2017 Classification of Pituitary Tumors – What is an Aggressive Pituitary Tumor?

M. Beatriz S. Lopes[1], Federico Roncaroli[2], Ann McCormack[3], Gerald Raverot[4]

[1]Department of Pathology, University of Virginia School of Medicine, Charlottesville, VA, USA; [2]Division of Neuroscience and Experimental Psychology, Faculty of Biology, Medicine and Health, University of Manchester, UK; [3]Department of Endocrinology, St Vincent's Hospital and Garvan Institute of Medical Research, University of New South Wales – Australia; [4]Department of Endocrinology, Hospices Civils de Lyon Cancer Research Centre of Lyon, Lyon 1 University, France

Tumors of the pituitary gland and sellar region represent approximately 15% of all brain tumors. Several categories of tumors may involve the sellar region, reflecting its complex anatomy. The most common tumors are, by far, the pituitary adenomas. The 4th Edition of the World Health Organization (WHO) Classification of Tumors of the Pituitary Gland (2017)[1,2] has made substantial changes in the classification of pituitary neuroendocrine (i.e. pituitary adenomas) and non-neuroendocrine tumors involving the pituitary gland. These changes include: 1) a novel approach for classifying pituitary neuroendocrine tumors according to pituitary adenohypophyseal cell lineages; 2) changes in the histological grading of pituitary neuroendocrine tumors with the elimination of the term "*atypical adenoma*;" and 3) re-definition of old entities like the null-cell adenoma and introduction of new entities like the *pituitary blastoma*.

The 2017 WHO classification recommends that pituitary adenomas should be histologically classified based on immunohistochemistry (IHC) for pituitary hormones, pituitary-specific transcription factors (mainly PIT-1, SF-1, and T-PIT), and other IHC markers commonly used in pathology practice. Only rarely is the ultrastructural analysis of the tumors necessary for their classification. Significantly, a new definition of null-cell adenomas is recommended by the WHO 2017 classification; these adenomas are now defined as adenomas that do not exhibit immunoreactivity for both pituitary hormones and pituitary transcription factors.[3] It is expected that the 2017 WHO classification of pituitary tumors will establish more biologically and clinically uniform groups of tumors, make it possible for practicing pathologists to better diagnose these tumors, and contribute to our understanding of clinical outcomes for patients harboring pituitary tumors. However, whether this translates into improved patient outcomes remains to be determined. Furthermore, the additional immunohistochemical complexity requires significant input by an expert neuropathologist and further evaluation of proposed diagnostic algorithms is required.[4,5]

The identification of pituitary neuroendocrine tumor that are likely to recur, behave aggressively or metastasize remains one of the most challenging problems in pituitary pathology.[5,6] Aggressive pituitary tumors and pituitary carcinomas both exhibit high mortality rates and Ki-67 index alone is unable to distinguish aggressive pituitary tumors and pituitary carcinomas.[7] Clinical and neuroimaging criteria including cavernous sinus and bone invasion are currently regarded as more reliable prognostic biomarkers than pathological features[8] and this reflects on treatment strategies.[7]

In the previous edition of the WHO Tumor Classification of Endocrine Organs (2004), the pituitary neuroendocrine tumors were divided into *typical adenoma*, *atypical adenoma*, and *carcinoma*. Atypical adenomas were defined as adenomas with histological features suggestive of an aggressive clinical behavior including histological atypia, elevated mitotic index, a Ki-67 labeling index greater than 3%, and overexpression of the p53 protein by IHC. Using these criteria, the incidence of atypical adenoma is relatively variable (2-15%). Its diagnosis criteria have not been uniformly applied and, most significantly, its prognostic value has not yet been established despite more than 15 years of its designation. In the WHO 2017 classification, the term of *atypical adenoma* is no longer recommended.[1] Evaluation of tumor proliferation potential, by mitotic count and/or Ki-67 labeling index, and tumor invasion is strongly recommended on individual case basis to identify clinically aggressive adenomas. The 2017 WHO classification does emphasize the identification of specific variants of adenomas associated with higher risk for recurrence. These include the sparsely-granulated somatotroph adenoma, lactotroph adenoma in men, Crooke's cell adenoma, silent corticotroph adenoma, and plurihormonal PIT-1 positive adenoma. The classification reiterates the definition of pituitary carcinomas as tumors demonstrating metastatic spread by either craniospinal dissemination or systemic metastases.[6]

The removal of the definition of "atypical adenoma" has left a void in the diagnosis of those lesions that may have aggressive potential. It must be remembered that the original proposal of "atypical adenoma" comes from the contraction of the descriptive definition of "adenoma with uncertain malignant potential" that was introduced by Pernicone et al in 1997.[9] This definition was not meant to establish an entity but was intended to warn clinician of the possibility of a more aggressive behavior.

A myriad of biomarkers have been proposed over the last 20 years, but only mitotic count and proliferation index measured with MIB-1 seem to offer to good reproducibility and good prognostic power. Although it requires further validation, the most reasonable attempt so far to provide clinicians with a prognostic indicator has been proposed by Trouillas and colleagues in 2013.[10] This 5-tier approach combines pathological features including mitotic count, MIB-1 labelling index and p53 status with the extension of the tumor.

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BL, FR, AMC and GR have no relevant relationships to report.

ACROMEGALY

Chairs: Annamaria Colao & Lisa Nachtigall

AC has no relevant relationships to report; LN receives grant support from Ipsen and investigator support from Chiasma.

New Drug Classes for Treating Acromegaly

Susan L. Samson

Department of Medicine, Section of Endocrinology, Diabetes and Metabolism, Department of Neurosurgery, Baylor College of Medicine, Houston, TX, USA

The main goal of medical therapy for patients with a somatotroph tumor is to control growth hormone and IGF-1 levels to improve morbidity and mortality. Currently approved injectable medications include somatostatin receptor ligands (SRLs) and a growth hormone receptor antagonist (GHRA). Additionally, some patients with mildly elevated GH/IGF-1 levels may respond to oral dopamine agonists. Combination therapy using the different drug classes is an additional option to achieve control. However, there is a significant proportion of patients in whom we do not achieve hormonal or radiologic control of the tumor. Also, patient choices for drug delivery are limited to injections, for the most part. The desire for more options and more efficacious therapies has driven discovery in the field so that there are a number of pipeline therapies for acromegaly. The majority of these are not a new class per se, as the primary mechanism of action is activation of the somatostatin receptors on the somatotroph tumor cells. Rather, the molecule may be novel (Somatoprim) or the mode of delivery is new (oral delivery of octreotide, new depot matrices, subcutaneous implants). Injection of GHR anti-sense RNA, to lower IGF-1, also is under investigation for clinical application.

SS is a PI for Chiasma and Novartis.

Personalized Approach to Acromegaly Management: Precision Medicine in Acromegaly

Manuel Puig-Domingo

Germans Trias Health Sciences Research Institute, Badalona, Spain, Endocrinology and Nutrition, Germans Trias University Hospital, Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

The need for precision medicine is driven by the heterogeneous nature of many diseases, and also this is the case of acromegaly. The current treatment algorithms for acromegaly are based upon a "trial and error" approach in which first generation somatostatin receptors ligands (SRL) are always the first-line medical therapy or as second-line therapy in patients undergoing unsuccessful surgery. However, because a high percentage of about 50% therapeutic failure, the inclusion of robust biomarkers identifying therapeutic response to SRL in the clinical guidelines is highly awaited. Such an approach would allow for a quicker achievement of disease control, better quality of life in the patient and would potentially cost-beneficial. At present, information coming from adenoma T2 MRI signal, octreotide GH suppression test and SSTR2, E-cadherine and Ki-67 immunohistochemistry among other biomarkers, has improved the capacity of predicting SRL response. The accumulated data on different markers is highly promising for including in therapeutic algorithms, provided that large scale assays may validate prospectively this approach. The validation trials will contribute to establish the standardization of measurement of the different biomarkers and hopefully will allow also to define cut-off values, a crucial step for final application to the clinical practice in the therapeutic decision process.

MPD receives honoraria from Ipsen, Novartis and Pfizer, research support from Novartis, and has participated in clinical trials for Chiasma and Novartis.

New Insights in Acromegaly: Prevalence, Presentation, Age and Gender

Adriana Ioachimescu

Department of Medicine, Division of Endocrinology and Metabolism, Department of Neurosurgery, Emory University School of Medicine, Atlanta, GA, USA

Prevalence rates of acromegaly have increased in studies published since 2001. Responsible factors include different case searching methodology, improved precision of biochemical assays, increased detection of pituitary incidentalomas, improved survival in patients with controlled acromegaly, and possibly a true increase in disease occurrence.

In adults, acromegaly equally affects both genders with a median age 40-47 years at diagnosis. Onset is usually insidious with a delay of 5 years or more from the initial manifestations. Although classic presentation with acral enlargement and coarsened features remains predominant, an increasing number of patients is diagnosed with acromegaly during work-up for hypogonadism or pituitary incidentaloma.

Biochemical markers of acromegaly inversely correlate with age. Women are older at diagnosis, which may be attributed to the delay in suspecting acromegaly and their lower IGF-1 levels compared with men. Some but not all studies found higher GH levels and larger tumors in women. Gender differences can be explained by the opposite effects of estrogen and androgens on hepatic GH receptors, while the influence of gonadal steroids on GH-secreting tumors remains to be clarified.

Most studies do not implicate age and gender as predictors of surgical remission with the caveat of pooled analyses across different age and gender categories. One study points out premenopausal women have a higher percentage of large invasive tumors and lower surgical remission rates than men. The relationship between acromegaly, gender and survival is complex: standardized mortality ratios are higher in women with acromegaly, but age at death is younger in men than women with acromegaly. In addition, age and gender influence glucose metabolism and to some extent the response to medical treatment in acromegaly.

The spectrum of clinical presentation and the impact of age and gender on biochemical and radiological parameters are important to consider for timely diagnosis and tailored treatment plans in patients with acromegaly.

AI has no relevant relationships to report.

Where Are We for Combination Treatments?

Sebastian Neggers

Erasmus University MC, Rotterdam, Netherlands

In general, treatment of acromegaly with (first generation) long-acting somatostatin analogues (LA-SRIF) can achieve complete normalization of growth hormone (GH) and insulin-like growth factor I (IGF-I) in roughly 40% of patients[1.] Different combinations have been reported. LA-SRIFS with dopamine agonists, can normalize IGF-I in patients with slightly to moderate elevated IGF-I levels(<150% of the upper limit of normal, independent of prolactin co-secretion)[2]. Combination of LA-SRIF and pegvisomant (PEGV), a growth hormone receptor antagonist, can normalize IGF-I levels in virtually all patients, independent of prior IGF-I levels, providing that the adequate dose of PEGV is used[1,3]. The required PEGV dose varies significantly between individual acromegaly patients, but seems to be lower in combination then during monotherapy[1,3]. One of the advantages of the combination therapy is that tumor size control or even tumor shrinkage can be observed in a vast majority of patients. The main side effects of PEGV are lipohypertrophy and transient elevated liver transaminases[3].

Pasireotide long-acting release (PAS-LAR) is a second-generation multi-receptor somatostatin analog designed with a broader binding somatostatin receptor profile than first-generation LA-SRIF. PAS-LAR has a similar safety profile to LA-SRIF, with the exception of a higher incidence of hyperglycemia, of about 60–88% of patients treated with PAS-LAR. In combination PAS-LAR normalizes IGF-I levels in most acromegaly patients, with a 50% pegvisomant-sparing effect in patients previously controlled with from LA-SRIF with PEGV[4]. However, PAS-LAR treatment coincided with a high incidence of diabetes mellitus.

During the presentation, the different combinations will be discussed and in which patients they might provide the biggest benefits with least side effects.

Reference:

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SN is a consultant for Ipsen, Novartis and Pfizer.

TRANSLATIONAL SCIENCE

Chairs: Felipe Casanueva & David Clemmons

FC is a consultant for Pfizer & DC has no relevant relationships to report.

Functional Genomic Profile of Sporadic Pituitary Adenomas

Anat Ben-Shlomo

Department of Medicine, Division of Endocrinology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Unlike for familial pituitary tumors, genomic drivers of tumorigenesis in sporadic pituitary adenomas are largely unknown. We prospectively collected and studied 159 sporadic pituitary adenomas for whole exome analysis, including 90 gonadotroph or null cell, 8 silent corticotroph, 10 functioning corticotroph, 16 lactotroph, and 35 somatotroph adenomas.

All pituitary adenomas exhibited a low mutation load, regardless of functional status. Strikingly, functioning pituitary adenomas secreting ACTH, GH, or PRL frequently harbored medium to high rates of somatic copy number variation (sCNV), including deletions and amplifications, commonly of an entire chromosome, while nonfunctioning gonadotroph/null cell adenomas usually did not exhibit sCNV. PRL and GH immunostaining positively correlated with sCNV score, while FSH and LH immunostaining, as well as adenoma suprasellar extension, correlated negatively with sCNV score.

Pathway enrichment analysis of somatic single gene CNV (sgCNV) identified the Fanconi anemia pathway as significant in somatotroph and functioning corticotroph adenomas, but not in gonadotroph/null cell adenomas or prolactinomas. In addition, 90% of somatotroph adenomas positive for *GNAS* mutation (29% of all somatotroph adenomas) exhibited medium-level sCNV. Moreover, somatotroph adenomas showed lower levels of PDE4D mRNA as compared to both gonadotroph/null cell and lactotroph adenomas, suggesting reduced cAMP clearance in these adenoma cell types. Following on these results, we examined cAMP pathway effects on DNA damage in normal mouse primary pituitary cultures. Forskolin and the long-acting GHRH agonist CJC-1295 increased intracellular cAMP together with induced GH production, and the addition of the PDE4 inhibitor rolipram further enhanced this response. Both forskolin and CJC-1295 also induced DNA damage in normal mouse pituitary cultures evidenced by increased phosphorylated H2AX (γH2AX) and by Comet assay results, an effect similarly enhanced by addition of rolipram.

Following the observed Fanconi anemia sgCNV deletions in BRCA1, BRCA2, and REV3L, in an attempt to recapitulate adenoma pathways, we knocked out BRCA2 in primary WT pituitary cultures. Intracellular cAMP was further induced upon GHRH treatment, as was gene expression of GH,and production of GH.

We conclude that increased sCNV in sporadic functioning somatotroph adenomas reflective of increased DNA damage occurs partly as a result of increased cAMP activity. These results provide a functional link between adenoma cell-selective DNA damage and excess GH production.

ABS has no relevant relationships to report.

Functional Effects of Pituitary Protein Sumoylation

Eduardo Arzt

Instituto de Investigación Biomedicina de Buenos Aires, Argentina (IBioBA)-CONICET- Partner Institute of the Max Planck Society

Using the mRNA differential display technique comparing tumor and normal pituitary cells we have found in clones of the tumoral lactosomatroph GH3 cell line overexpressing the cytokine IL-6 signal transducer gp130 and with enhanced tumorigenecity in nude mice, the expression of a novel gene RWD-containing sumoylation enhancer (RSUME or RWDD3).

RSUME expression is induced under hypoxic conditions, increases VEGF and HIF expression, which correlates with increased angiogenic potential of prolactinomas and has a potential role during vascularization. Its mechanism of action involves the stabilization of proteins through the post-translational modification sumoylation. One of its targets is PTTG. No mutations, epigenetic modifications or other mechanisms that deregulate and explain PTTG overexpression and action as an oncogene have been found so far. PTTG protein tight regulation and stabilization by RSUME/SUMO post-translational modifications accounts for its deregulation, abundance and pathogenic action in pituitary tumors.

EA has no relevant relationships to report.

Mechanisms for Immunotherapy-induced Pituitary Damage

Yutaka Takahashi

Division of Diabetes and Endocrinology, Kobe University Graduate School of Medicine, Kobe, Japan

Because of expanded indication of immune checkpoint inhibitors (ICI), the number of ICI-induced hypophysitis has markedly increased. It has been reported that the frequency of ICI-induced hypophysitis is 0.5-17.0%. The clinical characteristics of hypophysitis are different depending on the ICI. Headache associated with a transient pituitary enlargement is frequently observed although visual field defect is rare in CTLA-4 in inhibitors. In contrast, general fatigue and appetite loss associated with central hypoadrenalism is predominant in PD-1/ PD-L1 inhibitors. Permanent impairment in ACTH secretion is most common and transient impairment in TSH and LH/FSH secretion are observed. It is important to appropriately diagnose and treat especially with central hypoadrenalism. Generally, a replacement therapy of hydrocortisone and continuation of ICI are recommended. The underlying mechanisms may be different depending on the ICI. I will review and discuss the updated information and show some unpublished data regarding the underlying mechanisms.

YT has no relevant relationships to report.

Immunotherapy and Pituitary Damage – Clinical Implications

Alexander Faje

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Approved treatment indications for immune checkpoint inhibitors (CPIs) have expanded greatly in recent years and now include at least 15 different cancer types. The number of patients treated with these medications has increased in parallel. Hypophysitis is an immune-related adverse event (irAE) associated with CPIs, most frequently observed following anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) treatment but also occurring after therapy with agents targeting programmed cell death 1 (PD-1) and programmed death-ligand 1 (PD-L1). An increasing number of patients with this treatment complication have been encountered, and CPI treatment has likely become currently the most common etiology for hypophysitis. Glucocorticoid dosing strategies for CPI-associated hypophysitis may potentially impact malignancy treatment outcomes. Patients with hypophysitis secondary to CTLA-4 versus PD-1 blockade appear to have distinct clinical phenotypes, which lends indirect support to the proposal for different underlying mechanisms. It may be possible to redirect CPI-associated hypophysitis for therapeutic gain and exploit this irAE and CPIs for application in the treatment of aggressive pituitary tumors in selected patients.

AF has no relevant relationships to report.

MEET THE PROFESSOR CONCURRENT SESSIONS

Diagnosis of Nonpituitary Sellar Masses: An Integrative Approach

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The diagnosis of sellar and parasellar lesions which are not pituitary adenomas requires a multidisciplinary approach and comprehensive clinical, endocrinologic, ophthalmologic, neurologic, and radiologic tests. Since many of them lack characteristic clinical or imaging features, their adequate diagnosis is a real challenge[1]. The goal is to recognize them as accurately as possible before surgery and some clinical and imaging clues help to suspect non-adenomatous lesions[2, 3]. In many cases, the conclusive diagnosis can be made without surgery, and the appropriate therapy is chosen. However, in other cases, the morphological examination is necessary, and step-by-step studies are needed to reach the definitive diagnosis[4]. Occasionally, the final morphologic diagnosis is a real surprise. Sometimes, when the final diagnosis is reached, retrospectively, a small overlooked clue, essential for the analysis, is revealed. To avoid that, all clinical considerations should be considered to achieve a correct initial diagnosis.

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LS has no relevant relationships to report.

Management of Drug-induced Hyperprolactinemia

Philippe Chanson

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Hyperprolactinemia may be due to a variety of mechanisms, including direct stimulation of lactotroph cells (by estrogen for example) or, more frequently, a loss of the normally suppressive dopamine tone, releasing the brake on PRL secretion: this is the case of drugs that deplete the hypothalamus of its dopamine (e.g. reserpine and alpha-methyldopa, drugs that are no longer widely used) and drugs that block dopamine receptors on lactotroph cells i.e. dopamine antagonists such as phenothiazines (chlorpromazine), butyrophenones (haloperidol), pimozide, benzamides (sulpiride and metoclopramide). This is also the case of drugs that stimulate dopamine reuptake, such as imipramines and amphetamines.

Neuroleptics are the most frequent cause of drug-induced hyperprolactinemia. Sensitivity to these drugs varies markedly from one patient to another, in terms of both the PRL concentration and the duration of PRL elevation. The PRL level is generally below 100 ng/ml but concentrations up to 350 ng/ml have been described. During chronic treatment, 40-90% of patients have high PRL levels associated with clinical signs. The PRL level falls within 48 to 96 hours after neuroleptic discontinuation. Atypical antipsychotics induce a much smaller increase in PRL levels.

In general, treatment of hyperprolactinemia is not justified in the absence of menstrual disorders or altered libido: indeed, in women, if cycles are regular there is no risk of osteoporosis. The same applies for men, if testosterone levels remain normal. In these cases, antipsychotics can be pursued. Conversely, if premenopausal women are amenorrheic or if testosterone levels are low in men, the antipsychotic, either must be changed for another antipsychotic type (one with a less hyperprolactinemic effect), or, preferably (in particular if the control of the psychiatric condition is optimal) need to be pursued and sex steroids must be added in order to ensure adequate estrogen/testosterone impregnation.

When PRL levels are in the range of those found in patients with macroprolactinomas, MRI must be performed. In the very rare cases where a neuroleptic-treated patient also has a macroprolactinoma with suprasellar expansion compressing the optic chiasm, dopamine-agonists can be given very prudently. It may help to reduce the size of the macroprolactinoma and improve visual problems, without exacerbating the psychiatric condition. Obviously in that case, the objective is only to improve mass effect and not to normalize PRL levels.

PC has no relevant relationships to report.

Management of Residual Non-functional Adenomas After Surgery

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Non-functioning pituitary tumors are in general large, presenting with symptoms secondary to local pressure on adjacent structures. Transsphenoidal surgery is the first line of treatment for these tumors, but often they are not amenable to complete surgical resection. The optimal management of the post-operative residual mass is a matter of debate, and may include repeat surgery, radiation therapy and medical treatment. In this session we will explore these alternatives through clinical case discussions.

YG has no relevant relationships to report.

Perioperative Management of Patients with Cushing's Syndrome

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Optimal perioperative management of patients with Cushing' syndrome (CS), especially Cushing's disease (CD) remains controversial. The current rate of normalization of biochemical and clinical features for CD by transsphenoidal surgery varies from center to center, and is generally higher in specialized pituitary centers. A reliable determination of remission after surgery for CD continues to be challenging. Many different criteria are described in the literature; varying stringency and obtained at different post-operative timelines, with and without glucocorticoid replacement (GC) postoperatively. Therefore, an immediate remission interpretation needs to be assessed in a specific and individual-based context.

Postoperative GC treatment is not uniform among treatment centers. While physiologic replacement is the final goal of therapy for adrenal insufficiency, higher doses and prolonged GC tapering are commonly utilized, especially in patients with severe GC withdrawal symptoms.

While an initial CD diagnosis includes 24 hour urinary free cortisol (UFC), late-night salivary cortisol (LNSC) and overnight Dexamethasone test, recurrent CD diagnosis criteria are less well established. LNSC is an excellent tool for monitoring patients after pituitary surgery for CD and seems to detect hypercortisolism up to a year earlier compared with UFC in patients with disease recurrence. However, LNSC use also has several caveats, especially with new assay methods.

Endogenous CS is associated with significantly higher odds of developing venous thromboembolism (VTE). A recent meta-analysis, which includes case-series in addition to prospective and retrospective studies, showed that VTE risk (both non-operative and post-operative) in CS is significantly increased, odds ratio of spontaneous VTE in CS is 17.82 compared to healthy population. Postoperative

rates of VTE in CS are lower than in patients undergoing hip fracture surgery, a procedure well-known to carry a high VTE risk, but in which most patients require prophylactic anticoagulation. Nonetheless, definitive determination of risks and benefits of anticoagulation in CS is needed through large, prospective controlled trials. Exact timing (at diagnosis or before after surgery), type, doses and duration of thomboprophylaxis remains to be established. It is essential that endocrinologists consider very carefully the close association of CS with VTE when caring for patients and prophylactic intervention, and balance advantages of thromboprophylaxis with risk of bleeding on an individualized basis.

Medical treatment plays an important role for patients with CS who have persistent or recurrent disease after surgery, in whom surgery is not feasible, or in those awaiting effects of radiation. In many countries, preoperative use of medical therapy has also increased. Furthermore, use of adrenal steroidogenesis inhibitors preoperatively has been suggested to increase postoperative biochemical cure in CD, but further data is needed. In very severe cases, especially ectopic CS, where rapid control of the hypercortisolism is needed, IV etomidate has been successfully used; alternatively a combination of multiple adrenal steroidogenesis inhibitors (Ketoconazole/Metyrapone/Mitotane) has been reported to have high efficacy within days and with a similar safety pattern as single therapy.

This Meet the Professor session will include a case-based discussion of patients with CS; with a focus on pre- and post-operative management of patients with CD, including remission criteria, GC replacement, prophylaxis for VTE and preoperative treatment of severe CS.

MF is a consultant for Novartis and Strongbridge and her institution receives research support from Novartis and Strongbridge. EV has no relevant relationships to report.

Role of the "Bone Specialist" in the PTCOE

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With the aim of increasing the outcomes of pituitary disease management and, finally, enhancing patient care, a task force of the Pituitary Society recently published the criteria on which should be based the Pituitary Tumors Centers of Excellence (PTCOE) where a multidisciplinary team led by dedicated and experienced pituitary endocrinologists and surgeons should operate in collaboration with many other specialists.

Skeletal fragility and high fracture risk are a common, although often underdiagnosed, complication in patients with pituitary diseases characterized by hypopituitarism or hormonal hypersecretion. Therefore, the bone specialist should be included in the PTCOE to evaluate bone health in patients at diagnosis and during follow-up. In particular, this specialist may help on the diagnostic side in the study of bone metabolism selecting the optimal tools among bone markers (since bone loss is determined by an imbalance between bone resorption and bone formation), bone mineral density (BMD) measurements with classical dual energy X-ray absorptiometry (DXA) scans (although not good predictors of fracture risk) and vertebral morphometry: in fact, fragility fractures, and particularly vertebral fractures, are related to an impairment in bone quality more than in bone quantity, so they may even occur when bone mineral density (BMD) is not severely reduced. Finally, the bone specialist should advise on specific measures to prevent or treat bone loss in pituitary patients. What are the specific diseases in which the contribution of the bone specialist in the PTCOE is mandatory? First of all, acromegaly. In fact, it is well-known that growth hormone (GH) and insulin-like growth factor-I (IGF-I) excess significantly increases bone turnover markers with a deleterious effect on trabecular microarchitecture and highly increased risk of vertebral fractures with no predictive role of BMD. Recently, tools for investigating bone quality have been successfully tested in acromegaly, whereas pharmacological control of acromegaly has been shown to decrease fracture risk. Moreover, adult patients affected by hypopituitarism have shown a significant reduction in bone turnover markers, as an effect of GH deficiency, with high prevalence and incidence of vertebral fractures, that can be reduced when replacement therapy with rhGH is early prescribed. In addition, the bone specialist should take in to account the potential deleterious effects of L-thyroxine and glucocorticoids overtreatment on bone health.

Female, but also male patients with prolactin secreting adenomas, do frequently suffer from decreased BMD and increased risk of morphometric vertebral fractures. A question which remains open is the contribution of elevated prolactin per se to the skeletal risk; this may be relevant particularly in post-menopausal women with prolactinoma.

Also, in Cushing disease, chronic endogenous hypercortisolism exerts negative effects determining glucocorticoid-induced osteoporosis with suppressed bone turnover markers, BMD only slightly reduced or even normal in most of the cases and particularly with fractures as an early and very frequent event, which often represent the first clinical sign in this clinical setting.

Finally, we have recently reported an increased prevalence of radiological vertebral fractures in patients with TSH-secreting pituitary adenoma. In this rare condition, both age at diagnosis and hormone excess were determinants of vertebral fractures, whilst a medical pre-treatment with somatostatin analogues was shown to have a potential protective effect on skeletal health.

In conclusion, a wide range of pituitary diseases may require the active involvement of the bone specialist in the PTCOE. Use and choice of bone active agents in pituitary patients as well as personalized bone follow-up are the challenges that only a bone dedicated doctor in the multidisciplinary team may help to resolve.

SF receives honoraria from Ipsen.

The Challenge of "Pseudo-Cushing's"

John Newell-Price

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Aims:

1. To discuss the approaches to investigation of Cushing's syndrome at the mild end of the spectrum

2. To discuss the impact of interventions aimed at lowering or antagonising the effect of cortisol in conditions termed 'pseudo-Cushing's'

A pseudo-Cushing's state may be defined as some or all of the clinical features that resemble true Cushing's syndrome together with some evidence of hypercortisolism, but resolution of the underlying primary condition results in the disappearance of the Cushing's-like state. The term "pseudo-Cushing's" should, however be abandoned since there is hypercortisolism and the question is then whether this is physiological, pathological, and if the latter, autonomous.

Examples include pregnancy, chronic alcohol dependence, severe obesity, metabolic syndrome, poorly controlled diabetes mellitus, and major depression. In contrast, hypercortisolaemia may be present without features of Cushing's as found in anorexia nervosa, severe physical illness or stress, malnutrition, and chronic excess exercise.

Differentiating between mild true endogenous Cushing's syndrome and non-autonomous hypercortisolemia ("pseudo-Cushing's") can a considerable challenge. One key issue is to not perform any tests aimed at differential diagnosis of Cushing's syndrome unless the diagnosis of true autonomous hypercortisolemia, Cushing's syndrome, has been established.

There is overlap between the responses seen for all the standard tests used for the diagnosis of Cushing's syndrome pathological non-autonomous hypercortisolemia, and differentiation requires clinical judgement and at times, repeated assessment and time. Tests that have been reported to be of used include late night salivary cortisol, dexamethasone suppression tests with or without CRH, and desmopressin testing. None of the tests are perfect.

Questions remain as to the optimum management strategy for patients who do not have Cushing's syndrome but with activation of the HPA axis and hypercortisolism. Trials either lowering or antagonising the action of cortisol in patients with depression, non-alcoholic fatty liver disease and type II diabetes give insight into these questions.

JN-P is a speaker for HRA Pharma (fee paid to his University).

HOT TOPICS

Chairs: Eliza Geer and Maria Chiara Zatelli

EG receives research grants to MSKCC for participation in clinical trials from Novartis, Strongbridge Biopharma, and Ionis, and serves as a scientific consultant to Novartis, Strongbridge Biopharma, and Corcept Therapeutics. MCZ has no relevant relationships to report.

Reversibility of Impaired Brain Structures with Different Recovery Speeds in Short-term Cured Cushing's Disease: A Longitudinal Study Based on an Artificial Intelligence-assisted Tool

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Objective: Cushing's disease (CD) provides a unique model for assessing the effect of cortisol on human brains, with brain impairments caused by excessive cortisol; whether these impairments are reversible in cured CD after surgery has long been controversial for lack of high-quality longitudinal studies. Using by far the largest longitudinal brain analysis CD cohort, we assessed the reversibility of brain structure changes in CD after surgery and the correlation between clinical parameters. **Methods:** Fifty pathologically diagnosed CD patients and 36 matched healthy controls (HC) were enrolled in a tertiary comprehensive hospital and national pituitary disease registry center in China. 3T MRI and an artificial intelligence-assisted web-based auto-segmentation tool were used to quantify 3D brain volumes. Clinical parameters were collected for correlation analysis. All CD patients underwent transsphenoidal surgery (TSS), and short-term cured CD was measured over three months of post-operation follow-up. This study was approved by the Ethical Committee of PUMCH. **Results:** Widespread brain volume loss was observed in active CD patients compared with HC, including total gray matter ($P=0.003$, corrected with FDR), and frontal, parietal, occipital, temporal, insula, cingulate lobe, lateral and third ventricle respectively ($P<0.05$, corrected with FDR). All affected brain regions improved significantly after TSS ($P<0.05$, corrected with FDR). In short-term cured CD, total gray matter and most brain regions (except the frontal and temporal lobes) fully recovered and did not differ from those in HC ($P>0.05$, corrected with FDR). Adrenocorticotrophic hormone (ACTH) and serum cortisol changes were negatively correlated with brain-volume changes during recovery ($P<0.05$). **Conclusion:** These findings provide the first unequivocal, direct demonstration of the rapid reversal of total gray matter loss in short-term cured CD. The combination of fast recovery areas and slow recovery areas after TSS is consistent with the partial recovery of memory and cognitive function observed in clinical practice. Correlation analyses suggest that ACTH and serum cortisol levels are reliable serum biomarkers of brain recovery after surgery for clinical use.

The authors have no relevant relationships to report.

Functional Human Hypothalamus-Pituitary Co-Organoid as a Novel Therapeutic Discovery Tool for Acquired Hypopituitarism

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Objective: Our goal is to speed pituitary gland recovery and reverse pituitary dysfunction caused by acquired lesions including traumatic brain injury (TBI). We generated a functional human hypothalamus-pituitary co-organoid derived from induced pluripotent stem cells to enable drug screening for disrupted hypothalamic-pituitary axes. **Methods**: Starting with induced human pluripotent stem cells (iPSCs) and specific differentiation factors, we generated a hypothalamus-pituitary co-organoid. Specifically, iPSCs were grown for two weeks in E6 media supplemented with various pituitary-specific differentiation factors, including BMP4, SHH, FGF8, and FGF10. At various time points, supernatants were collected for ELISA assays and lysates were generated for RNA and protein analyses. **Results**: Based on features of human pituitary development, we have developed a method that differentiates human iPSCs into an hormone-secreting pituitary cell lineage, expressing pituitary-specific genes in 15 days. This was confirmed by measuring ACTH secretion by ELISA, and gene and protein expression analyses by qRT-PCR and western blotting, respectively. By day 15 ACTH concentrations were ~600 pg/ml. qRT-PCR revealed that expression of pituitary genes TBX19, POMC, PITX2, and CRHR1 was increased significantly between days 14 and 17 (19-790-fold compared to Day 0). Immunocytochemistry revealed that GH, ACTH, and TBX19 proteins were highly expressed in differentiated pituitary lines compared to undifferentiated ones. GH in differentiated cells had a cytoplasmic staining pattern compared to nuclear location of OCT4 control in undifferentiated cells. Importantly, co-culture of pituitary organoids and hypothalamic neurons grown on separate surfaces of a trans-well plate, synergistically increased GH (mRNA – 10 fold) expression and increased secretion of GH (ELISA – 3 fold) after co-culturing for 11 days. **Conclusion**: We have generated a functional human co-organoid comprising robustly functional hypothalamic and pituitary cells. This human model, which recapitulates hypothalamic-pituitary control of pituitary hormone production, enables mass screening for assessing both normal and disrupted hypothalamic-pituitary pathways in disease and injury.

The authors have no relevant relationships to report.

Exploration of Novel Treatment for Cushing Disease

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Cushing Disease (CD) is a life-threatening condition and current medical treatments are suboptimal. We used a novel ACTH AlphaLISA assay in a high throughput screen of a kinase inhibitor library (KIL, n=430) to identify corticotroph tumor-directed drugs that potently inhibit tumor proliferation and ACTH secretion. In murine corticotroph tumor AtT20 cells, 6, 20 and 115 compounds exhibited >50% inhibition of ACTH secretion and 36, 105 and 263 compounds inhibited proliferation in vitro by >50% at 100nM, 1mM and 10mM doses respectively. The PI3K/HDAC dual inhibitor CUDC-907 (MedChemExpress) was the most potent and inhibited AtT20 corticotroph tumor POMC mRNA expression by 56% (RT-PCR) and ACTH secretion (ELISA) by 50% at LC50 of 5nM. CUDC-907 was even more potent in human corticotroph primary cultures (n=3) where it demonstrated anti-proliferative effects and inhibited POMC mRNA by 77% and ACTH secretion by 31% at LC50 of 3nM. In an in vivo xenograft model of CD using AtT20 cells inoculated into athymic nude mice (Nu/J strain, Jackson lab), CUDC-907 (300mg/kg dissolved in Captisol) administered daily by oral gavage was well tolerated. CUDC-907 led to reduced tumor volume (TV (cm3), Control 0.17 ± 0.05 vs. CUDC-907 0.07 ± 0.02, $p<0.05$) and tumor weight (TW (gram), Control 0.1 ± 0.02 vs. CUDC-907 0.04 ± 0.006, $p<0.05$) by 65% and 56% respectively compared to vehicle-treated (Captisol) controls. Plasma ACTH (ACTH (pg/mL) Control 206.1 ± 27.2 vs. CUDC-907 47.4 ± 7.3, $p<0.05$) and corticosterone (Corticosterone (ng/mL) Control 180 ± 87 vs. CUDC-907 27 ± 4.66, $p<0.05$) levels were reduced by 77% and 85% respectively in CUDC-907 treated mice compared to controls. Given the efficacy we have demonstrated in in vitro and in vivo models of CD, combined with the proven safety profile and tolerance in clinical trials, we propose that CUDC-907 may be a promising novel therapy for CD.

The authors have no relevant relationships to report.

Safety of Once-weekly Somapacitan in Adult Growth Hormone Deficiency (AGHD): Data from a 53-week Open-labelled Extension of the REAL 1 Trial

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Objective: Somapacitan is a reversible albumin-binding GH derivative developed for once-weekly administration. The open-labelled extension of REAL 1 (NCT02229851) further investigated the efficacy/safety of somapacitan treatment in patients with AGHD for an additional 53 weeks following the initial 34-week phase and 1-week washout. We report safety data from the extension phase. **Methods:** In the main phase of REAL 1, 301 patients were randomized 2:2:1 to receive once-weekly somapacitan, daily somatropin, or once-weekly placebo. Patients who completed the main phase continued into the extension as follows: 1) somapacitan-treated patients continued their treatment, 2) somatropin-treated patients were re-randomized 1:1 to somapacitan or somatropin, and 3) patients receiving placebo were switched to somapacitan. Safety assessments included adverse events (AEs), injection site tolerability, and anti-drug antibody development. **Results:** 300 patients were included in the safety analysis. Similar proportions of patients reported AEs in the somapacitan/somapacitan (84.2%), somatropin/somatropin (88.5%) and placebo/somapacitan (80.3%) arms. Most AEs were mild (71.4%) and deemed unrelated to trial product. Most frequently reported AEs (frequency ≥5%) in the somapacitan/somapacitan arm included common GH related events such as nasopharyngitis, headache, back pain, gastroenteritis, upper respiratory tract infections, arthralgia, dizziness, peripheral edema, and vomiting. 12.3% of patients experienced 68 serious AEs, with 66 deemed unrelated to trial products. A total of 21 injection-site-related AEs were reported, equally distributed between the somatropin- and somapacitan-exposed patients. None of the injection site related AEs observed in the trial were deemed clinically significant, and all patients recovered during the trial period. No anti-somapacitan antibodies were detected. **Conclusions:** The safety profile of extended treatment with somapacitan for up to 86 weeks was favorable and comparable to that of daily somatropin and consistent with previously completed somapacitan trials. These findings provide further evidence that somapacitan is a well-tolerated once-weekly alternative to daily GH in AGHD.

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Ethical committee approval information: *Prior to trial initiation, the protocol, the consent form, and the subject information sheet were reviewed and approved according to local regulations by appropriate health authorities, and by an independent ethics committee (IEC)/institutional review board (IRB), i.e. a review panel responsible for ensuring the protection of the rights, safety and well-being of human subjects involved in a clinical investigation, which was adequately constituted to provide assurance of that protection. The IECs/IRBs were transparent in their functioning, independent of the researcher, the sponsor and any other undue influence, and duly qualified.*

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GROWTH HORMONE RESEARCH SOCIETY SYMPOSIUM

Chairs: Gudmundur Johannsson and John Kopchick

GJ receives honoraria from Eli Lilly, Novartis, Otsuka, Merck Serono, Novo Nordisk, Pfizer, Shire and Astra Zeneca; JK has no relevant relationships to report.

Criteria for Re-establishing the Diagnosis of GHD in Childhood Onset Patients During Transition and Assessment of Subsequent GH Responsiveness During Therapy

PE Clayton

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A young person who has been deficient in GH in childhood either as an isolated abnormality or as part of hypopituitarism needs to have their GH status re-evaluated at the completion of growth. In those with defined hypothalamic-pituitary pathology (^{3}4 pituitary hormone deficiencies) or an established genetic defect, a seamless continuation of GH treatment is appropriate. In all other cases in particular those with isolated GH deficiency, formal evaluation after at least 4 weeks off GH treatment, with a GH provocation test and IGF-I / IGFBP-3 levels, is required. A number of tests are used, including the insulin tolerance test (ITT), arginine, and GHRH + arginine. The criterion for GH replacement in adults has been set at a peak GH on ITT <3mg/L, but this cut-off is likely to be too low in the late teenage years when GH secretion is at its life-time peak in normal individuals. A range of peak GH cut-off levels have been proposed at transition between 5 and 7μg/L dependent on stimulus used with higher levels for GHRH + arginine. Isolated GHD encompasses a wide range of dysfunction in the GH axis and retest normal rates can be up to 80%: it has been proposed that for those without structural pituitary abnormalities retesting should be carried out in early puberty with discontinuation of GH therapy if testing is normal.

In those identified as persistently GH deficient, the transition period is a good opportunity to assess body composition, bone density, lipid profile and general health status using measures of 'Quality of Life' (although there is a need for validated measures in this age group). These young people should be offered GH treatment – there is no consensus on the restart dose, but pragmatically the dose used should be sufficient to keep the IGF-I level within the normal range. However, serum IGF-I primarily reflects hepatic IGF-I generation, and its use as a biomarker for metabolic or QoL parameters is not well defined. Genetic markers, such as the exon 3 polymorphism in the GH receptor gene, have been evaluated in adult GHD; however, the impact of this variant is modest. There is a major need to identify novel biomarkers (for example through genomic & proteomic approaches) that will reflect the diverse effects of GH therapy in these young people.

PC has no relevant relationships to report.

Tissue Specific Effects of GH Signaling in Human Subjects

Jens Otto Lunde Jørgensen

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In addition to its protein anabolic effects, which are IGF-I-dependent, GH stimulates lipolysis in adipose tissue (AT) and induces insulin resistance in skeletal muscle via direct effects. Moreover, the lipolytic and insulin antagonistic effects are causally linked based on strong experimental data. The molecular mechanisms underpinning these metabolic effects, however, remain elusive.

We have demonstrated that exposure to endogenous as well as exogenous GH induces phosphorylation of STAT5b after 30-60 minutes in both AT and skeletal muscle in human subjects *in vivo*. Taken together, this proves that a GH pulse in the circulation is followed by GH receptor signal transduction and gene transcription in both AT and skeletal muscle. In skeletal muscle, no clear evidence of crosstalk between GH and insulin signaling is recorded in human studies; instead, the insulin antagonistic effect involves suppression of PDHa activity indicating substrate completion between glucose and fatty acids. In human AT, we have recently shown that GH exposure both *in vivo* and *in vitro* suppresses an array of anti-lipolytic signals, including G0/G1 switch gene 2 (G0S2) and fat specific protein 27 (FSP27). Both proteins inhibits adipose triglyceride lipase, the lipolytic master switch, via different mechanisms. We have indirect evidence to suggest that the mechanisms involve GH-induced suppressed expression of G0S2 and FSP27 mRNA.

In conclusion, a systemic GH pulse induces GH signaling in both AT and muscle in human subjects in vivo. In both tissues, this evokes insulin-antagonistic effects in terms of reduced glucose uptake in muscle and suppressed anti-lipolysis in AT, respectively. Further mechanistic studies are needed.

JOJ is on the Advisory Board of Ipsen and Pfizer and has a research grant from Novartis.

Long Acting Growth Hormone Preparations

Andrew R. Hoffman

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Recombinant GH was introduced in 1985 as a daily injection for the treatment of GH deficiency. Since compliance with once-a-day dosing has led to less than optimal drug adherence, a number of longer-acting GH formulations have been produced using a variety of novel techniques. These include depot preparations, pegylated GHs, chimeric GH analogs that enhance duration of activity and GH analogs that can bind with serum albumen or other moieties. While many of these long-acting GH preparations are no longer being evaluated, several products are now in advanced stage human testing. We will review the history of long-acting GH preparations and describe potential benefits and risks associated with these new molecules.

AH is a consultant for Ascendis, Gene Science, Genexine, and Novo Nordisk.

The Continuum Between GH Deficiency and GH Insensitivity

Vivian Hwa

Division of Endocrinology, Cincinnati Center for Growth Disorders, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

The clinical conditions of congenital GH deficiency (GHD) and GHI share characteristics of minimal growth retardation *in utero*, severe postnatal growth retardation, dysmorphic and metabolic abnormalities, and markedly reduced serum concentrations of IGF-I. GHI is distinguished from GHD by demonstrated resistance to endogenous and exogenous GH in terms of growth, metabolic changes or significant elevation of serum IGF-I. In recent years, the clinical, biochemical and genetic characteristics of GHD and GHI has rapidly expanded beyond the "classical", to encompass milder forms of these syndromes. The greater awareness of these milder forms has been attributed, in part, to the advent of sophisticated genetic methodologies, including next-generation genomic sequencing. The spectrum of defects support the existence of a GHD and GHI continuum, with milder forms likely to be more prevalent than the classical.

VH has no relevant relationships to report.

JOINT SESSION WITH NURSES AND PATIENTS

Chairs: Anne Klibanski and Shlomo Melmed

AK receives consulting fees from Chiasma and Crinetics; SM has no relevant relationships to report.

Approval of Drugs for Orphan Indications and the Challenges of Rare Disease Drug Development

Peter P. Stein

Office of New Drugs, Center for Drug Evaluation and Research, FDA, Silver Springs, MD, USA

There are over 7000 known rare diseases, affecting about 1 in 10 individuals. Although there has been important progress over the past decades in finding new treatments for such disorders, the proportion of such diseases with effective treatments remains small. Approvals of orphan indications, one of the tools to encourage development of therapies for rare diseases, has increased over the past 10-15 years, as has the number of development programs for orphan products. There are unique challenges in development programs for rare disease drugs, including often limited understanding of the natural history of the disease, and the complexities and challenges of designing, conducting, and interpreting studies in small populations. FDA has a number of programs intended to facilitate and accelerate the development of drugs for serious diseases with unmet medical needs, and these are often applied to drugs for rare diseases. The presentation will discuss the challenges of rare disease drug development, how FDA applies regulatory flexibility to such programs, and the tools the Agency has that can facilitate development of drugs for rare diseases, including orphan approvals.

PS has no relevant relationships to report.

PANEL: Acromegaly Guidelines and Real-world Clinical Practice: Harmonization or Further Dichotomy

Daphne Adelman[1], Laurence Katznelson[2], Karen JP Liebert[3], Jill Sisco[4]

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Acromegaly management requires a multidisciplinary approach to ensure all aspects of care are appreciated and addressed. A multidisciplinary team can address the unique needs of each individual patient, and assure maximal patient education. The medical care team is composed of an endocrinologist, neurosurgeon, radiation therapist, other medical specialists depending on presence of co-morbidities, and nursing with expertise in pituitary disorders. In addition, there are acromegaly patient communities who offer a range of support for patients, including medical information, networking communities, and blog sites: all with the goal to promote education and enhance patient knowledge and advocacy. During this session, a panel that includes an endocrinologist, pituitary nursing, and an acromegaly community patient advocate will discuss a multidisciplinary approach to topics including challenges in diagnostic testing, appropriate targets for therapy (particularly if biochemical targets and symptomatic targets do not match), and how to assess for quality of life outcomes. Thus, the panel will discuss approaches to common challenges experienced by patients with acromegaly.

DA is on an Advisory Board for Pfizer and is a consultant for Crinetics; LK is a consultant for Chiasma and Pfizer; KJPL is a consultant for Pfizer, Chiasma and Ono Pharma; JS is a consultant for Pfizer.

Patient Reported Outcomes and Clinical Assessment Tools: Refinement of Acromegaly Treatment Goals

Nienke Biermasz

Department of Medicine, Leiden University, Leiden, Netherlands

Acromegaly is a disease caused by GH and IGF-I overproduction, usually due to a pituitary adenoma. Multimodality treatment is usually required to treat the GH adenoma, the symptoms and co-morbidity of acromegaly. The aim of treatment is to normalize IGF-I and GH, parameters that are reflective of restoration of the GH/ IGF-I axis and consequent improvement in morbidity, mortality and quality of life. However, clinical and patient reported outcome parameters are increasingly considered to be important in addition to biochemical parameters. They may be concordant to biochemistry but sometimes are different from the biochemical situation. How to measure, when to measure, and what to do with those patient reported outcomes is still matter to debate. In the presentation I will review current patient reported outcome measures, available instruments and recently developed clinical assessment tools. I will discuss their place in clinical practice and research and report on own experience.

NB has no relevant relationships to report.

CRANIOPHARYNGIOMA

Chairs: Odelia Cooper and Niki Karavitaki

OC and NK have no relevant relationships to report.

Genetics of Craniopharyngiomas

Cynthia Lilian Andoniadou

King's College London, UK

Craniopharyngiomas are epithelial tumours of the sellar region derived from the pituitary, with an overall incidence of 1.86 new cases per million people per year. Although histologically benign, subgroups can behave aggressively, leading to high morbidity. The two types, adamantinomatous (ACP) and papillary (PCP), predominantly occur in children and adults, respectively. These two tumours do not share a common cause, but both lack neuroendocrine differentiation. ACP are characterised by recurring gain-of-function mutations in *CTNNB1*, activating the WNT signalling pathway, and most PCP by *BRAF-V600E* mutations leading to activation of MAPK signalling. This talk will describe recent molecular and transcriptomic advances in the study of these tumours and provide evidence from animal models relating to their pathogenesis and promising therapeutic avenues.

CLA has no relevant relationships to report.

Surgical and Radiosurgery Approaches

Pietro Mortini

PM has no relevant relationships to report.

Preserve or Sacrifice the Stalk? Endocrinological Outcomes, Extent of Resection and Recurrence Rates Following Endoscopic Endonasal Resection of Craniopharyngiomas

Theodore H. Schwartz

Weill Cornell Medical College, Neurosurgery, Otolaryngology and Neuroscience, New York, NY, USA

Object: Gross-total resection of craniopharyngiomas (CPs) is potentially curative and is often the goal of surgery, but endocrinopathy generally results if the stalk is sacrificed. In some cases, GTR can be attempted while still preserving the stalk, however, stalk manipulation or devascularization may cause endocrinopathy and this strategy risks leaving behind small tumor remnants that can recur.

Methods: A retrospective review of a prospective cohort of patients who underwent initial resection of CP using the EEA over a period of 12 years at Weill Cornell Medical College, New York-Presbyterian Hospital was performed. Post-resection integrity of the stalk was retrospectively assessed using operative notes, videos and post-operative MRI. Tumors were classified based on location into Type I (sellar), Type II (sellar-suprasellar) and Type III (purely suprasellar). Pre- and post-operative endocrine function, tumor location, body mass index (BMI), rate of GTR, radiation, and complications were reviewed.

Results: A total of 54 endoscopic endonasal procedures for first time resection of CP were identified. The stalk was preserved in 33 (61%) and sacrificed in 21 (39%). GTR was achieved in 24 (73%) patients with stalk preservation and 21 (100%) patients with stalk sacrifice ($p=0.007$). Stalk preservation surgery achieved GTR and maintained completely normal pituitary function in only 4/33 (12%) patients. New hypocortisolemia and hypothyroidism occurred in 42.3% and 48% of patients with stalk preservation and 88.2% and 88.2% following stalk sacrifice ($p=0.004$ and $p=0.01$, respectively). Permanent post-operative diabetes insipidus was present in 16 patients (49%) with stalk preservation and in 20 patients (95%) following stalk sacrifice ($p=0.002$). In the stalk preservation group, rates of progression and radiation were higher with intentional STR or NTR compared to GTR (67% vs. 0%; $p<0.001$ and 100% vs. 12.5%; $p<0.001$ respectively). Tumor recurrence/progression occurred in 9 (27.3%) in the group with stalk preservation and in 1 (5%) following stalk sacrifice ($p=0.038$). However, for the subgroup of patients in whom GTR was achieved, stalk preservation did not lead to significantly higher rates of recurrence (12.5%) compared with those in whom it was sacrificed (5%; $p=0.61$) and prevented anterior pituitary insufficiency in 33% and DI in 50%.

Conclusion: While the decision to preserve the stalk reduces the rate of postoperative endocrinopathy by roughly 50%, nevertheless significant anterior and posterior pituitary dysfunction often ensues. The decision to preserve the stalk does not guarantee preserved endocrine function and comes with a higher risk of progression and need for adjuvant therapy. Nevertheless, attempts should be made to preserve the stalk if GTR can be achieved to reduce post-operative endocrinopathy.

TS has no relevant relationships to report.

Oxytocin Effects in Childhood-onset Craniopharygioma Patients

Hermann L. Müller

Department of Pediatrics and Pediatric Hematology/Oncology, University Childrens Hospital, Klinikum Oldenburg, Oldenburg, Germany

Background: Quality of survival of childhood-onset craniopharyngioma (CP) patients is frequently impaired by hypothalamic involvement (HI) or treatment-related sequelae such as obesity and neuropsychological deficits. Oxytocin (OXY), a peptide hormone produced in the hypothalamus and secreted by posterior pituitary gland, plays a major role in regulation of behavior and body composition.

Methods: In a cross-sectional study, OXY saliva concentrations were analyzed in 34 long-term CP survivors with and without HI or treatment-related damage, recruited in the German Childhood Craniopharyngioma Registry, and in 73 healthy controls. OXY was measured in saliva of CP patients and controls before and after standardized breakfast and associations with gender, body mass index (BMI), HI, diabetes insipidus, and irradiation were analyzed. Furthermore in a pilot study, emotion recognition abilities were analyzed with regard to OXY concentrations in saliva and urine before and after nasal administration of 24 IU OXY in 10 CP patients with proven hypothalamic lesions (4 patients with grade I: limited to anterior hypothalamic areas; 6 patients with grade II: involving mammillary bodies and posterior hypothalamic areas). Perception and identification of emotional expressions in voices was tested using the Geneva Multimodal Emotion Portrayals (GEMEP) corpus and current mental state was assessed by Multidimensional Mood Questionnaire.

Results: In cross-sectional analysis, patients with preoperative HI showed similar OXY levels compared to patients without HI and controls. However, patients with surgical hypothalamic lesions grade I (anterior hypothalamic area) presented with lower levels ($p=0.017$) of OXY under fasting condition compared to patients with surgical lesion of posterior hypothalamic areas (grade II) and patients without hypothalamic lesions (grade 0). CP patients' changes in OXY levels before and after breakfast correlated ($p=0.02$) with their BMI. In our pilot trial, nasal administration of OXY was well tolerated and resulted in increased OXY concentrations in saliva and urine. After OXY administration, patients with postsurgical lesions limited to the anterior hypothalamus area (grade I) showed improvements in emotional identifications compared to patients with lesions of anterior and posterior hypothalamic areas (grade 2). Focusing on correct assignments to positive and negative emotion categories, patients improved assignment to negative emotions.

Conclusions: CP patients continue to secrete OXY, especially when anterior hypothalamic areas are not involved or damaged, but OXY shows less variation due to nutrition. OXY might have positive effects on emotion perception in childhood-onset CP patients with specific lesions of the anterior hypothalamic area. Further studies on larger cohorts are planned in the context of the German Craniopharyngioma Registry.

Supported by the German Childhood Cancer Foundation, Bonn, Germany

HM has no relevant relationships to report.

CUSHING'S SYNDROME

Chairs: Anthony Heaney and Fahrettin Keleştemur

AH and FK have no relevant relationships to report.

Epigenetic Control of Pituitary Gene Expression

Jacques Drouin

Institut de recherches cliniques de Montréal, Montréal, Canada

The chromatin landscape defines the parts of the genome that are available for gene expression. In complex multicellular organs such as the pituitary where different cell fates are established during development, epigenetic control of the chromatin landscape is critical to establish individual cell identities. Having defined the accessible chromatin landscape of the various mouse pituitary lineages and correlated this landscape with cell-specific gene expression, we find that it is essentially the accessible enhancer landscape, rather than promoters, that define pituitary cell identities. Few epigenetic regulators are known: these are transcription factors that direct the remodeling of the epigenome to implement new cell fates and they accomplish this through recruitment of enzymatic chromatin remodeling complexes. In the pituitary we showed that the pioneer factor Pax7 specifies the intermediate pituitary and melanotrope cell fate through chromatin opening of a set of about 2500 enhancers. The mechanisms underlying this pioneering activity will be discussed in the context of Pax7 interaction with Tpit that determines the POMC fates and directs terminal differentiation of the two POMC lineages. During pituitary development, the interplay between the tissue specifying Pax7 and the cell differentiation determination gene Tpit is critical for establishment of the unique cell identities of the two POMC lineages.

JD has no relevant relationships to report.

Advances in Cushing Disease Medical Therapies

Beverly MK Biller

Department of Medicine, Harvard Medical School; Neuroendocrine Unit, Massachusetts General Hospital, Boston, MA, USA

Cushing's disease (CD) is associated with significant morbidity and increased mortality if untreated. However, effective management can improve co-morbidities and lower mortality risk. While the first line of treatment for CD is surgery performed by an expert pituitary surgeon, some patients are not in remission and others may develop a later recurrence, so additional therapeutic options are needed.

A number of new medications for CD have been evaluated over the past decade. Some have been approved for use, and others are still under investigation. These include medications available for other indications, a long-acting version of an approved treatment, new compounds related to older adrenal-blocking medications, and novel agents. Recently discovered mechanisms of corticotroph tumorigenesis have raised the possibility of new targets for treatment.

Medications currently available for the management of CD include those targeting the pituitary gland to decrease ACTH secretion, others that decrease cortisol production at the adrenal level, and one that blocks glucocorticoid receptors in target tissues. This presentation will review developments in medical therapy for CD over the last 10 years and touch on investigational agents. Advances in the past decade offer the promise of better management for our patients with this challenging disorder.

BMKB serves as the principal investigator of research grants to Massachusetts General Hospital from Novartis and Strongbridge Biopharma and receives consulting honoraria from Novartis and Strongbridge Biopharma.

Surgery for the Invisible Tumor in Cushing Disease

Kalmon D. Post

Department of Neurosurgery, Mount Sinai Medical Center, New York, NY, USA

The remission rate for CD with adenomas that are visible on MRI vary from 62 – 100%. However, the remission rate for non-visible adenomas varies from 50 – 86%. Clearly there is more difficulty in finding the adenoma during surgery when it is not evident on imaging.

Utilize the best quality 3T MRI with dynamic imaging.

Inferior petrosal sinus sampling (IPSS) does not reliably identify the tumor site with a prediction of accurate laterality of at best 70%. Hemihypophysectomy based on IPSS lateralization may have a remission rate of no better than 50%.

Improved detection of microadenomas with imaging techniques would dramatically improve results. 3T imaging with ½ dose gadolinium may improve detection. Composite methionine PET/ 3.0 T MR imaging may improve identification of microadenomas.

The roles of Intraoperative cytology and frozen section techniques have been questioned.

Intraoperative ACTH measurements have been performed as a means of knowing if the adenoma has been resected.

The possibility of intraoperative labeling of adenomas with different techniques such as 5-ALA and other optical fluorescence agents has been researched.

Other instrumentations such as microdopplers and ultrasound have been utilized to identify the adenoma.

However, the bottom line currently may still be the experience of the neurosurgeon in appreciating the adenoma visually during surgery.

KP has no relevant relationships to report.

Adrenal Stem Cells and Pathogenesis of Adrenal Cushing's Disease

Gary Hammer

Departments of Internal Medicine (Metabolism, Endocrinology & Diabetes), Cell & Developmental Biology, and Molecular & Integrative Physiology, University of Michigan, Ann Arbor, MI, USA

The long-range objective of our laboratory is to understand the cellular and molecular mechanisms by which signaling pathways and downstream transcription factors coordinate the specification of adrenocortical cells within the adrenal gland. The adrenal cortex is a critical endocrine organ that mediates the mammalian stress response through the robust modulation of steroid output in response to physiologic demand. While it is becoming increasingly clear that paracrine factors are critical to adrenal progenitor cells proliferative maintenance, how endocrine signals are integrated with these inputs to coordinate adrenal steroidogenesis and zonation (differentiation) remains poorly defined.

The nuclear receptor Steroidogenic Factor 1 (SF1) is the master regulator of both adrenocortical proliferation and differentiation. In the absence of SF1, the adrenal fails to develop and death results without steroid replacement. The cellular and physiologic context in which SF1 engages in unique transcription programs to mediate these processes is completely unknown. Although previous studies have defined *Shh*-positive cells embedded in the peripheral cortex as the self-renewing progenitor population that differentiates into functional steroidogenic cells, the paracrine and endocrine mechanisms that regulate this process is undefined. The mechanisms by which these multipotent renewing cells are maintained during adrenal homeostasis will be discussed – specifically how SF1 mediates lineage renewal (self-renewing proliferation) in the progenitor cells, and how paracrine and endocrine signals regulate progenitor cell lineage renewal versus lineage conversions (differentiation) under physiological conditions.

GH has no relevant relationships to report.

ABSTRACTS

POSTER PRESENTATIONS

APPETITE/OBESITY

P1

Posterior Hypothalamus Sparing Surgery and Outcome of Patients with Severe Initial Hypothalamic Involvement of Childhood Craniopharyngioma: Results of KRANIOPHARYNGEOM 2007

Agnieszka Bogusz[1,2], Svenja Boekhoff[1], Monika Warmuth-Metz[3], Gabriele Calaminus[4], Maria Eveslage[5], Hermann L. Müller[1*]

*[1]Department of Pediatrics and Pediatric Hematology/Oncology, University Children's Hospital, Klinikum Oldenburg AöR, Oldenburg, Germany; [2]Department of Endocrinology and Diabetology, The Children's Memorial Health Institute, Warsaw, Poland; [3]Department of Neuroradiology, University Hospital, Würzburg, Germany; [4]Department of Pediatric Oncology and Hematology, University Hospital, Bonn, Germany; [5]Institute of Biostatistics and Clinical Research, University of Münster, Münster, Germany; *on behalf of study committee KRANIOPHARYNGEOM 2007*

Background: Quality of survival (QoS) is frequently impaired in patients with childhood-onset craniopharyngioma (CP) by hypothalamic syndrome. The debate, whether pretreatment hypothalamic involvement (HI) has apriori prognostic impact or treatment-related hypothalamic lesions (HL) determine outcome, is controversial. **Methods:** In cross-sectional prospective study, survival and outcome of 109 CPs recruited 2007–2014 in KRANIOPHARYNGEOM 2007 with reference-confirmed presurgical, anterior plus posterior HI were analyzed with regard to surgical HL (no, anterior or anterior plus posterior HL). Body mass index (BMI), QoS assessed by PEDQOL, and functional capacity (FMH) were measured at diagnosis, during follow-up, and at last visit (median follow-up: 6 years). **Results**: Surgical HL were reference-confirmed in 86 of 109 (79%) CP (29 anterior, 57 anterior+posterior HL). PFS and BMI at diagnosis were similar in CP subgroups with different degree of HL. CP with anterior plus posterior HL presented with higher BMI at one year follow-up (median BMI: +5.21 SD) and at last visit (BMI: +5.74 SD), when compared to patients without HL (BMI, one year: +1.72 SD, p=0.001; last visit BMI: +2.27 SD, p<0.001) and when compared to patients with anterior HL (BMI, 1 year: +2.46 SD, p=0.002; last visit: +2.87 SD, p=0.001). QoS improved during follow-up in CP without HL for physical functionality (p=0.047), emotional stability (p=0.040), and social functionality (p=0.002) when compared to CP with anterior plus posterior HL. Functional capacity was not associated with degree of HL. **Conclusions**: Based on appropriate preoperative staging, posterior hypothalamus-sparing surgical strategies do not increase risk for relapse/progression, improve QoS and ameliorate development of obesity in CP at risk for obesity due to presurgical anterior plus posterior HI.

The authors have no relevant relationships to report.

CELLULAR & MOLECULAR ACTION

P2

A Proteomic Snapshot of Recurrent Non-functioning Pituitary Adenomas

Pinaki Dutta[1], Ashutosh Rai[2], Anil Bhansali[1], B.D. Radotra[3], Rajesh Chhabra[4], S.K. Gupta[4]

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Non-functioning pituitary adenomas (NFPA) may be locally invasive and also recurrent. Markers of recurrence are needed to guide patient management. To examine proteomic expression pattern of recurrent NFPAs, we recruited 20 patients, grouped them as non-invasive (n=5), likely-invasive (n=5), invasive (n=5), non-recurrent (n=5), and recurrent (n=5). Histopathological, radiological, and surgical findings were used to classify invasion while follow-up of 15 years was used to determine the recurrence. We performed quantitative proteomics analysis using LC-MS/MS-Orbitrap Fusion™ Tribrid™ Mass Spectrometer on tumor tissues. Up to 5 precursor ions were selected for MS/MS. Data were analyzed using MASCOT and SEQUEST software. Criteria for calculating p-values of peptides include a) fold change and b) multiple peptides. In case of such proteins, permutation test was applied by random sampling of 1 to n number of peptides. For random peptide ratios, sub-sampling was performed. *In-silico* tools like, Gene Ontology, DAVID, and KEGG were used to determine the biological significance. In this quantitative proteomic approach, we identified 31880 and 30512 peptides and 5202 and 5150 proteins in replicate 1 and replicate2 respectively. Recurrent adenomas were biologically active with 235 overexpressed and 22 under expressed proteins. Principle component analysis (PCA) showed 97.1% variance in recurrent NFPAs as compared to non-recurrent, while there was only 8.3% variance in between the non-recurrent groups. We observed >5-fold overexpression of MYH2, CKM, MYH7, MPZ, KRT75, MYLPF, MYL1, ENO3, EIF4H, DES, TNNC2, TCEB2, PMP2, KRT19, COL1A1, COL1A2, TAC1, CPA3, and MYH13. Gene ontology analysis suggested 7.1-fold enrichment of Rho GTPase pathway (p=0.0013) in recurrent NFPAs. TUBB2B, TUBB2A, TMN1, MDK, NCALD, RPL36A, RPS29 were under expressed in recurrent NFPAs. PCA analysis of under expressed proteins revealed only 59.6% variability between non-recurrent and recurrent groups and 40.3% variance in between the non-recurrent group. Results shows distinct protein expression patterns in recurrent NFPAs, which could serve as biomarker and may have therapeutic implication.

The authors have no relevant relationships to report.

P3
Exosome-transmitted lncRNA H19 Inhibits the Growth of Pituitary Adenoma

Yong Zhang[1*], Yan Ting Liu[1,2*], Hao Tang[1*], Zhe Bao Wu[1]

*[1]Department of Neurosurgery, Center of Pituitary Tumor, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [2]Department of Neurosurgery, First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; * These authors contributed equally to this work.*

Background: Exosome vesicles (EVs) mediate communication between cells, and are involved in the responsiveness to anticancer therapies. Our previous study indicates that long non-coding RNA H19 expression is frequently downregulated in human primary pituitary adenomas and negatively correlated with tumor progression (Nature Communications, 2018). However, the role of exosomal lncRNA H19 in the inhibition of pituitary tumor growth remains unclear. **Objective:** To investigate whether exosomal H19 can be transported across the cell membrane to exert its inhibitory effect on pituitary tumor growth. **Methods:** The EV GH3 cells with or without H19-overexpression were used to establish a xenograft model. The indicated protein levels were confirmed by immunohistochemistry assay and Immunoblot analysis. Isolated exosomes were identified by transmission electron microscopy, nanoparticle tracking and Western blotting. Immunofluorescence assays were performed to assess the expression of exosomal H19 in EV GH3 cells and H19-overexpressin cells. The expression levels of serum exosomal H19 from the 20 healthy subjects and 206 patients with various subtypes of pituitary tumors were detected by ultracentrifugation and qRT-PCR. Blood samples of patients were obtained from Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. Ethical approval was obtained from the institutional ethics committee of Medical School of Jiao Tong University. **Results:** The growth of distal tumor cells was inhibited by transferring exosomal H19, which can be transported through the tumor microenvironment and cell membrane and exert its inhibitory effect. Cabergoline could increase H19 expression and played a synergic therapeutic effect with exosomal lncRNA H19. Mechanistically, exosomal H19 inhibits phosphorylation of mTORC1 substrate 4E-BP1 without affecting the S6K1 phospharylation. Of note, the expression level of exosomal H19 in the patients with all subtypes of pituitary tumors was significantly lower than that in the healthy subjects. The change of exosomal H19 level may be correlated with the prognosis or drug response of the patients; that is, a higher exosomal H19 level after DA treatment may predict a good prognosis. **Conclusion:** Exosomal H19 inhibits the growth of pituitary tumors through inhibiting the 4EBP1 phosphorylation. The plasma exosomal H19 may serve as an important biomarker for predicting medical response of patients with prolactinomas.

The authors have no relevant relationships to report.

CRH/ACTH/CUSHING'S

P4
A Phase 2 Multicenter, Open-Label Study of Oral Seliciclib in Patients With Cushing Disease

Ning-Ai Liu[1], Garni Barkhoudarian[2], John Carmichael[3], Anthony Heaney[4], Daniel Kelly[2], Ronald Swerdloff[5], Christina Wang[5], Shlomo Melmed[1]

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Background: Cyclin E overexpression is unique to corticotroph tumors in the pituitary, and contributes to tumor growth, uncontrolled POMC transcription, and autonomous ACTH production. Our preclinical investigations led to identification of seliciclib (R-roscovitine), a purine analog and CDK2/cyclin E inhibitor that causes cell cycle arrest and apoptosis in corticotroph tumors, as well as rapid suppression of POMC gene expression and ACTH production independent of cell cycle inhibitory effects. Preliminary data from a small, pilot phase 2 study of oral seliciclib in Cushing disease demonstrated promising responses in measurements of 24-hour urinary free cortisol (UFC). **Study Methods:** We are conducting a phase 2 multicenter, open-label clinical trial to evaluate safety and efficacy of seliciclib in adult patients with newly diagnosed, persistent, or recurrent Cushing disease. Primary endpoint is normalization of UFC or ≥50% reduction of UFC from baseline. Up to 30 subjects will be treated for 4 weeks with oral seliciclib given 4 consecutive days each week. The trial uses an adaptive design to evaluate two of three sequential dose cohorts (400 mg BID, 300 mg BID, or 800 mg/d in 3 divided doses as 300/250/250 mg) based on efficacy outcomes. **Discussion:** Our published preclinical studies and preliminary clinical data in patients with Cushing disease revealed rapid response of pituitary corticotroph tumors to seliciclib treatment with suppressed POMC gene expression, ACTH production, and UFC levels. This rapid inhibition enables a short phase 2 efficacy trial and allows us to enroll patients planning to undergo surgery or other pituitary- or adrenal-targeted therapies without compromising standard of care. The goal of this trial is to find the lowest dose of seliciclib with evidence of efficacy and safety, which will provide basis for future larger clinical studies of this novel and highly targeted agent for Cushing disease.

ClinicalTrials.gov Identifier: NCT03774446. Funding Source: R01FD006106.

The authors have no relevant relationships to disclose.

P5
ACTH-dependent Pulmonary Carcinoid: Two Challenging Cases and Review of Literature

Arwa Elsheikh, Jonven Attia, Michael Nead, Moises J. Velez, Inga Harbuz-Miller, G. Edward Vates, Ismat Shafiq

University of Rochester Medical Center, Rochester, NY, USA

Ectopic ACTH-dependent Cushing syndrome is a very rare disease with significant diagnostic and treatment challenges. Pulmonary carcinoid accounts for about 50 % of the cases. Our two recent cases highlighted the challenges of this condition. **Case 1**: A 35-year-old woman presented with ACTH-dependent Cushing syndrome. She had a stable right pulmonary nodule since 2012. Pituitary MRI showed a right-sided 4 mm microadenoma, but IPSS confirmed an ectopic source. Chest CT showed the pulmonary nodule was smaller. Octreotide, FGD PET and Ga-68 dotatate scans were negative, but transbronchial biopsy of the pulmonary nodule followed by wedge resection confirmed ectopic ACTH producing typical carcinoid tumor. After surgery, she was stabilized with octreotide and metyrapone. **Case 2**: A 41-year-old man was diagnosed with ACTH-dependent Cushing syndrome in 2004. MRI head was normal, and IPSS confirmed an ectopic source. CT chest showed a right pulmonary nodule with uptake on octreotide scan. He underwent right thoracotomy and pathology confirming oncocytic type carcinoid tumor. He was lost to follow up until 2016. He had worsening edema, hypokalemia, HTN, fatigue while on glucocorticoid physiologic dose in spite of bilateral adrenalectomy and gastric bypass. CT abdomen showed right adrenal hyperplasia. CT chest showed no obvious lesion but octreotide scan showed uptake in the mediastinal region. He received radiation to the right hilar region followed by octreotide treatment. He is stabilized on glucocorticoid replacement and monthly octreotide. Adrenalectomy may seem an attractive option to control hypercortisolemia secondary to ACTH dependent pulmonary carcinoid but failure is common. Pulmonary surgery is the main stay of treatment with better chances of cure can be achieved with aggressive tumor resection and lymphadenectomy. Medical treatment remains essential to control hypercortisolemia along with surgery.

MN is a consultant for Medtronic. The other authors have no relevant relationships to report.

P6
Circadian Peripheral Clock System Imbalance in Cushing's Disease

Vinicius Reis Soares, Clarissa Silva Martins, Leonardo Domingues Araujo, Silvia Liliana Ruiz Roa, Lucas Ravagnani Silva, Ayrton Custodio Moreira, Margaret de Castro

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Context: Glucocorticoids circulating levels in healthy individuals oscillate according to a circadian rhythm, influenced by the molecular system of clock genes. In Cushing's syndrome, there is an altered cortisol daily rhythm, which can be associated to disruption of clock genes rhythmic expression. **Objective:** Evaluate the expression of clock genes (*CLOCK, BMAL1, CRY1, CRY2, PER1, PER2, PER3*) in peripheral blood mononuclear cells of healthy individuals and in patients with Cushing's disease. **Design, Setting and Participants**: Case-control study approved by the Ethical Research Committee of the University Hospital of the Ribeirao Preto Medical School, University of Sao Paulo, comprised by female Cushing's disease patients (n=12) and controls (n=13). **Main Outcome Measures:** Participants underwent salivary cortisol measurement at 0900h and 2300h. Peripheral blood samples were obtained at 0900h, 1300h, 1700h, and 2300h for assessing clock genes expression by qPCR. **Results**: In healthy controls, there was a circadian variation for *CLOCK*, *PER1* and *PER3. CLOCK and PER3,* but not *PER1,* were in phase alignment with cortisol circadian rhythm. In patients, there was a loss of the pattern of clock genes circadian variation in concomitance with the loss of cortisol circadian rhythm. One exception was *CRY2*, which presented higher expression at night in patients. **Conclusions:** Our data suggest that the loss of normal circadian cortisol rhythm is associated to dysregulation of circadian clock genes expression in Cushing's disease. Hypercortisolism and circadian clock genes deregulation might contribute to metabolic features of Cushing's disease.

The authors have no relevant relationships to report.

P7
Corticotroph Cell Adenoma Mimicking Ectopic Cushing's Syndrome: A Case Report

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Background: Crooke cell adenoma is the least common and the most aggressive type of corticotroph adenomas. The rapid progression of the disease sometimes puts the diagnosis into a challenge. **Clinical Case:** A 66-year old female patient admitted to a health center with complaints of headache, vision loss and dropping of the left eyelid within 2 days. The physical examination revealed pupillary anisocoria, no light reflex, third, fourth and sixth cranial nerve palsies and total loss of vision on left eye and ptosis of the left eyelid. A 21x19mm pituitary macroadenoma was seen on brain CT imaging. The patient was referred to our outpatient clinic for further diagnosis and treatment. At admission, the patient was hypertensive and hyperglycemic. The laboratory tests revealed hypokalemia (K: 2,9mmol/L) and leukocytosis (WBC: 13800/mm^3). She was hospitalized to make the definitive diagnosis and to correct the electrolyte imbalances and hyperglycemia. At sellar MR imaging, a 45mm macroadenoma extending inferiorly to sphenoid sinus and clivus, anteriorly to nasal cavity and superiorly to 3rd ventricle and had marked bleeding inside. At follow up, there was a very rapid progression of the symptoms of the eyes and the right eyelid also dropped and vision was impaired. The pre-operative hormonal status was revealed as ACTH: 1133pg/ml, Cortisol: 63,44µg/dl and the other pituitary hormones were in normal limits. The patient underwent emergent endoscopic trans-sphenoidal pituitary adenomectomy and the pathology was determined as "Crooke's cell adenoma". Post-operatively, the hypokalemia and hyperglycemia resolves, vision and ptosis on right eye ameliorated but the symptoms on the left eye remained the same. **Conclusions:** The progression of the symptoms may be very rapid and aggressive in patients with Corticotroph cell adenoma as it may mimic the ectopic Cushing's syndrome.

The authors have no relevant relationships to report.

P8
Cushing's Disease and Ectopic Cushing's Syndrome Diagnosed 22 Years Apart

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Objective: Probability of developing two primary ACTH-secreting-tumors is calculated at approximately 7.4cases/trillion. A case of a patient with both pituitary and pancreatic ACTH-secreting tumors (ectopic CS, ECS) is presented. **Clinical Case:** A 46-year-old female presented (1996) with new onset visual loss, headache and was diagnosed with pituitary macroadenoma. Subsequent transsphenoidal surgery (TSS) confirmed CD and was followed by conventional radiation. In 2008, urine free cortisol (UFC) was elevated, MRI showed pituitary microadenoma and CD confirmed by inferior petrosal sinus sampling); a 2nd TSS ensued. Postoperatively; no clinical adrenal insufficiency (AI), 24hr UFC 12 µg/dL and ACTH 44pg/dL. In 2014, presentation with severe weakness, emotional liability, and weight gain. ACTH 152 pg/dL, 24 hr UFC 13,120 µg/dL, midnight salivary cortisol 832 µg/dL, whole body octreotide scan and pituitary MRI were unremarkable. Further surgical options were refused; cabergoline 1.5 mg/twice/week and pasireotide 0.6µg/twice/day, were prescribed. UFC and ACTH normalized. In 2017, due to AI symptoms and persistent low–normal UFC, cabergoline was stopped and after 18 months pasireotide slowly decreased (600µg/twice/day–300µg/twice/day–300µg/daily), then stopped; UFC normal for 5 months. The patient presented to emergency in spring 2018 with confusion, generalized weakness, 18lb weight loss, orthostatic hypotension, K 1.9mEq/dL and new-onset diabetes; ACTH 100pg/dL, 24-hr-UFC 13,280 µg/dL. Ga-68-DOTA-PET/CT revealed a pancreatic body mass suspected as a NET. Subsequently, the patient underwent bilateral adrenalectomy and distal pancreatectomy (pathology consistent with a NET staining ACTH/SSTR2positive). One and 6 month-postoperative ACTH 36pg/mL. **Discussion:** Though the octreotide scan was negative we cannot exclude that the 2014 episode was ECS rather than CD. The ECS' pasireotide response can be explained by SSTR-positive receptors in pancreatic tumor. **Conclusion:** To our knowledge this is second reported case of pathology- proven-CD that developed ECS years on. Reestablishing CS etiology is necessary in some patients with a complex clinical and biochemical picture.

MF is a consultant for Novartis and Strongbridge and her institution receives research support from Novartis and Strongbridge. The other authors have no relevant relationships to report.

P9
Cushing's Disease in Men: A 20 Year Single Center Experience

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Objectives: To examine gender-specific outcomes in Cushing's disease (CD) treated with transsphenoidal selective adenomectomy (TSA). **Methods:** Retrospective review of 108 consecutive CD patients operated between 1994-2014. Statistical analyses included Fisher's exact, Wilcoxon test and Kaplan Meier survival analyses. **Results**: Men (M) represented 13.8% (N=15). Mean age was 46±13 M (vs 40±12 Women, p=0.077). Hypopituitarism affected 73% M (vs 46% W, p=0.09). Prevalence of hypertension (86.7% M vs 65.5% W) and diabetes (46.7% M vs 40.8% W) were similar. Mean preoperative urine and serum cortisol levels were comparable (139±74 mcg/day M, 245±308 W; and 24.6±15 mcg/dL M, 24.8±13 W). Mean ACTH levels were similar (80.5±65 pg/mL M, 75±46 W). MRI indicated a microadenoma in 53.3% M (vs 64.5% W), macroadenoma in 20% (both genders) and no adenoma in 26.7% M (vs 15% W). Cavernous sinus invasion was present in 20% M (vs 6.4% W, p=0.1). Nadir postoperative serum cortisol was reached after 3.0±1.9 days M (vs 3.8±1.3 W); a level <5mcg/dL was achieved in 80% M and 75% W. At 3 months postoperatively, 86.7% M and were normo- or hypocortisolemic (vs 90.3% W), and glucocorticoid replacement was used by 73.5% M (vs 77.4% W). Median follow-up was 4.3 years. None of the men experienced CD recurrence (vs 18.6% W, p 0.07). Reoperation was performed in 6.6% men (vs 19.35% W), and radiation in 13.3% M (vs 18.3% W). Two men (13.3%) and 2 women (2.1%) died at a mean of 3.7 and 2.8 years postTSA respectively (p 0.008). Of them, one man and one woman were in remission postoperatively, while the other two required radiation. **Conclusions:** Although CD rarely affects men, our study outlines possible gender-differences regarding presentation and long-term course, including mortality. Further multicentric studies including a higher number of men are necessary.

The authors have no relevant relationships to report.

P10
Gamma Knife Radiosurgery in Pituitary Adenomas: Argentinean Experience

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The aim of our study was to evaluate efficacy and safety of Gamma Knife radiosurgery (GKRS) in patients with pituitary adenomas and to analyze predictors of remission. **Materials and methods**: We performed a retrospective analysis of our patients with pituitary adenoma treated with GKRS between 2002 and 2017. Those with less than 1 year of follow-up were excluded. We evaluated: epidemiological and clinical data at diagnosis, biochemical remission (for secreting tumors) and tumor control rates, effect latency and associated complications. We defined biochemical remission as the normalization of hormonal levels (IGF-1 in acromegaly and 24 hours urinary free cortisol in Cushing's disease), without concomitant medication in all cases. We considered tumor control as the reduction (>20%) or stability of the remnant. Data were analyzed with Stata version 12.1. **Results**: We studied 99 patients, 51 acromegalic, 28 with non-functioning adenoma (NFA), 15 with Cushing Disease (CD) and 5 with other pituitary tumor types. 91% were treated after unsuccessful surgery. Median margin dose was 29.3, 19.6, 30.6 and 26.2Gy respectively. Median follow-up was 63 months (12-235). Global tumor control rate was 94%. Global biochemical remission rate was 55%, higher in acromegaly than in CD (OR 4.7, 95%Ci 2.1-10.4, P<0.0001), with a median remission latency of 29.5 months (6-156). In acromegalic patients, lower pretreatment IGF-1 levels were significantly associated with higher remission rate (OR 0.99, 95%Ci 0.997-0.999, P=0.009). No other significant prognostic factor to remission was found. The main adverse effect was hypopituitarism (26%); patients with CD were more prone to develop loss of pituitary function after GKRS (OR 2.93, 95%Ci 1.2-7.2, P=0.019). **Conclusions**: Stereotactic radiosurgery with Gamma Knife is an effective and safe therapeutic option for patients with postoperative persistent or recurrent pituitary adenomas potentially aggressive and/or resistant to pharmacological treatments.

The authors have no relevant relationships to report.

P11

Hypercoagulability in Cushing's Syndrome (CS): Prevalence of Symptomatic Thrombotic/ thromboembolic Events in a Single-center Retrospective Study

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Background: Hypercoagulability is associated with Cushing's syndrome (CS); up to odds ratio 18 (95% CI 14-22) for venous thromboembolism (VTE) in CS vs. normal population. Outcomes in patients with CS with/without anticoagulation treatment remains unclear. Methods: Retrospective review (July 2006–August 2018) of symptomatic arterial/venous thromboembolism prevalence in a consecutive series of CS patients at a single-center. **Results:** 208 cases: 186 Cushing's disease (CD), 5 ectopic CS (ECS), 17 adrenal CS (ACS); 165 female, age at presentation 44.4years (±14.7), BMI 33.9 (±8.38); 186 underwent transsphenoidal surgery (TSS) and 45 unilateral/bilateral adrenalectomy (BLA). Thromboembolism was found in 39 patients (18.2%), 32 females; 13 deep vein thrombosis (DVT), 16 cerebrovascular accident, 8 pulmonary embolism, 12 myocardial infarction. 11 patients had >1 thromboembolic event. Patients with thromboembolism; 35 CD, 4 ECS, treatment was TSS in 35, BLA in 15 and 1 on medical therapy. Mean age 50 years (±12.2) and BMI 33 (±8.4). **Thromboembolic risk factors:** 15 tobacco use and 17 diabetes mellitus. At time of thromboembolic event 26 patients (66%) were eucortisolemic/hypocortisolemic on hydrocortisone; 3 (9.4%) were on estrogen. 22 patients were on testosterone replacement, of these 3 had a thromboembolic event. Thromboembolism occurred 48.3 months pre-surgery in 23.7%, and 58.6% patients developed DVT within 65 days post-operatively. **Discussion:** Despite inherent retrospective study limitations, we found a high (~20%) prevalence of clinically symptomatic thromboembolisms in CS; 84.6% of patients were not anticoagulated and 12.8% were on short–term pre- and post-operative prophylactic anticoagulation. Prophylactic anticoagulation 1 week pre-operatively and up to 28 days post-operatively has been reserved for high–risk patients. Optimal duration of anticoagulation remains unknown. **Conclusion:** Increased awareness of thromboembolism in CS is highly desirable. Both prognostic coagulation studies and clinical risk factors remain elusive. Further prospective investigations are required to optimize anticoagulant protocols along with individualized pre-operatively assessments of thromboembolism and bleeding risk.

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P12

Levoketoconazole in the Treatment of Endogenous Cushing's Syndrome: Secondary Endpoint Results from a Phase 3 Study (SONICS)

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Objective: To assess the safety and efficacy of levoketoconazole in the treatment of endogenous Cushing's syndrome (CS), with a focus on selected secondary endpoints related to cortisol measurements. **Methods:** In a phase 3, open-label, IRB-approved dose-titration study, adults with confirmed CS and mean 24-hour urinary free cortisol (mUFC) ≥1.5 × ULN were treated with levoketoconazole in 3 phases: 2- to 21-week dose-titration phase (150 to 600 mg BID as needed, to target mUFC normalization), 6-month maintenance (M) phase, and 6-month extended evaluation. The primary endpoint, mUFC normalization at end of maintenance (EoM), was presented previously (Fleseriu M, et al. ENEA 2019). Select secondary endpoints reported here included percentage of complete responders (mean mUFC ≤ULN) at all monthly visits in M, and changes from baseline in mUFC and late night salivary cortisol (LNSC) levels. **Results:** Ninety-four patients enrolled: median (range) age, 44.0 (18-75) years; 80 (85%) had Cushing's disease diagnosis. Percentage of complete responders ranged from 30% to 50% during monthly visits in M. Mean mUFC and LNSC levels decreased significantly from baseline to M1 visit (Day 30 of M) and remained lower than baseline through EoM. Decreases in mUFC levels (mean baseline value: 218.2 µg/day; mean change from baseline range: -134.1 to -171.8 µg/day) were paralleled by decreases in LNSC levels, which infrequently

normalized (mean baseline value: 0.43 µg/dL; mean change from baseline range: -0.19 to -0.24 µg/dL by visit). The most common AEs were nausea (32%) and headache (28%). Four patients experienced serious AEs considered study drug–related (elevated liver function tests, n=1; prolonged QTc interval, n=2; adrenal insufficiency, n=1). Alanine aminotransferase increased >3 × ULN in 11% of patients, which reversed with drug discontinuation. **Conclusions**: Levoketoconazole treatment led to sustained reductions in both mUFC and LNSC levels in this population with CS. **Support:** Strongbridge Biopharma.

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This abstract includes discussion of product(s) unlabeled (off-label) for use as approved by the FDA.

P13
Long-term Follow-up of a Patient with an Invasive Corticotropinoma: The Challenge of Curing Cushing's Disease

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In 2006 a 20-year-old woman was referred to the Endocrinology Division to rule out Cushing's Syndrome. She had Cushing's phenotype, arterial hypertension. Menarche: 15 years old, only 2 menses, 5-year amenorrhea. Lab test: Urinary free cortisol (UFC): 377 ug/24 hrs. (20-100), Midnight salivary cortisol (MSC): 0.64ug/dl (0.07-0.43), 8-hrs. Cortisol: 34 ug/dl (7-25), ACTH: 65 pg/ml (<54), Overnight 1 mg Dexamethasone suppression test (DST): cortisol: 29 ug/ml, 8 mg DST: plasma cortisol: 15 ug/ml, IGF-I level below normal. The remaining hormones and visual field were normal. MRI showed a pituitary microadenoma with invasion of right cavernous sinus surrounding carotid artery. Ketoconazole 800 mg/day was indicated. In November 2006 a trans-sphenoidal surgery with incomplete removal was performed. There was no immunostaining. July 2007: stereotaxic radiotherapy: 5000 cGy was performed. She began with ketoconazole 1 g/day and cabergoline: 0.5 mg/week. November 2008: she remained active, so we decided to perform a left adrenalectomy, laparoscopic approach; pathology: adrenal hyperplasia. November 2010: a right adrenalectomy was performed by open approach, the patient began with hydrocortisone replacement, but it was stopped because of normal cortisol levels. In abdominal TC small nodules compatible with remaining left adrenal gland were visualized. ACTH levels increased after bilateral adrenalectomy but began to decrease in the last 2 years. Currently, the patient has subnormal MSC, normal UFC and serum cortisol, ACTH 297 pg/ml, the tumor is smaller than at diagnosis. Conclusion: The presence of hyperplastic adrenal cells prevented Nelson syndrome and adrenal insufficiency; the patient needs adrenal replacement only in stressful situations. Treatment of patients with Cushing's disease and invasive tumors is extremely difficult and needs a multidisciplinary approach.

The authors have no relevant relationships to report.

P14

Low Diagnostic Utility of Ga-68-DOTATATE PET/CT in Localization of Ectopic ACTH-secreting Tumors: Single Center Clinical Experience and Literature Review

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Objective: Gallium-68-DOTATATE, DOTATOC, or DOTANOC positron emission tomography/computed tomography (Ga-68-DOTA-PET/CT) reportedly exhibits better sensitivity in identifying ectopic ACTH-secreting tumors (ECS) tumors not visible on conventional imaging; a single-center experience is reported. **Results:** Six consecutive patients with confirmed active ECS (mean follow-up 21.5 months; range 1-53 months) who underwent Ga-68-DOTA-PET/CT are reported. One patient had a suspicious 3.5cm pancreatic mass on CT and Ga-68-DOTA-PET/CT showed decreased uptake; pathology confirmed a grade 1 ACTH+pancreatic neuroendocrine tumor (NET). One patient had a 2.1cm adrenal and suspicious 1.1cm lung nodule (cryptococcoma on pathology) on CT. Subsequent, Ga68-DOTA-PET/CT showed low-grade equivocal adrenal uptake. Four other patients had normal/non-suspicious CT, octreotide scan, and FDG-PET while Ga-68- DOTA -PET/CT was normal/non-specific uptake. Three of 6 patients underwent bilateral adrenalectomy, 2 are biochemically controlled with medication and one is awaiting surgery. A literature review identified 29 articles (mainly case-reports and case-series) on Ga-68-DOTA-PET/CT in ECS patients; Ga-68-DOTA-PET/CT identified 35/47 (74%) overt lesions by CT. When conventional imaging was negative, Ga-68-DOTA-PET/CT identified 17/26 (65%) lesions; 3 were false-positives. **Discussion:** Ga-68-DOTA-PET/CT has emerged as a highly sensitive imaging modality for NETs, especially for occult tumors. Previous systematic imaging review for ECS showed Ga-68-DOTA-PET/CT sensitivity being similar to CT (81.8%) in histologically-proven cases and 100% in covert-cases (no occult cases were reported). Our literature review demonstrated that Ga-68-DOTA-PET/CT was 65% diagnostic in initially occult lesions, while 9/26 remained occult. In our case-series, Ga68-DOTA-PET/CT was suggestive in 1 NET case and did not help identify a culprit lesion in 5/6 patients. Thus, we suggest literature on Ga-68-DOTA-PET/CT in ECS is subject to reporting bias, and false-negatives are likely underreported. **Conclusion:** Our single center experience and literature review demonstrate lower than previously reported sensitivity of Ga-68-DOTA-PET/CT for ECS, especially in occult lesions. Diagnostic value for ECS needs further study.

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P15

Neuromedin B Receptor Antagonist Suppress Pomc Expression and Cell Proliferation in AtT-20 Cells

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Objective: We previously reported that Neuromedin B (NMB) is expressed in mouse pituitary corticotrophs in adrenal insufficiency (Kameda H. Endocrinology 2014). Because NMB is also expressed in several cancer cells and stimulates ACTH secretion, we have hypothesized that NMB is related to proliferation and hormone secretion of corticotroph adenoma. To elucidate the hypothesis, we investigated the effects of NMB receptor antagonist in AtT-20 cells. **Methods**: *in vitro* experiments. We extracted mRNA and protein from AtT-20 cells after incubation with 1μM NMB receptor antagonist PD168368, performing real-time qPCR and western blotting to investigate Pomc expression. The survival of AtT-20 cells was assessed after the PD168368 treatment. *in vivo* experiments. We transplanted one million AtT-20 cells in the back of athymic nude mice subcutaneously and administrated PD168368 by intraperitoneal injection. After two weeks of treatment, we analyzed the size of transplanted tumors and blood ACTH concentration. The animal experiments were approved by the Institutional Animal Care and Use Committee of National University Corporation Hokkaido University. **Statistics**: Comparisons between two groups were made using unpaired Student's t-tests. One-way ANOVA was employed to compare values among multiple groups. If the ANOVA test showed significant differences, the Tukey-Kramer post hoc test was employed to compare two specific groups. **Results**: Pomc mRNA and protein expression were suppressed with 1μM PD168368 by 55±3 % and 38±4 %, respectively. AtT-20 cell survival was decreased by 40±8% after 72 hours incubation with 1μM PD168368. PD168368 (1.2 mg/kg per day) administration reduced transplanted tumor growth compared with vehicle group (after 2 weeks: 15.0±0.8 mm vs 11.1±1.1 mm, $p<0.05$) and decreased blood ACTH concentration (432±56 pg/mL vs 102±34 pg/mL, $p<0.05$). **Conclusion**: NMB receptor antagonist suppressed Pomc expression both *in vitro* and *in vivo*, suggesting that it could be a potential treatment for Cushing disease.

The authors have no relevant relationships to report.

P16
Safety and Efficacy of Early Postoperative Acetylsalicylic Acid for the Prevention of Venous Thromboembolism After Transsphenoidal Surgery for Cushing Disease

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Introduction: Venous thromboembolism (VTE) risk is increased in Cushing Disease (CD), occurring in up to 3.8% of patients[1]. Although VTE risk may be compounded by the immobilization and inflammation of transsphenoidal surgery (TSS), some neurosurgeons refrain from early antiplatelet / anticoagulant use due to concern for hemorrhage. We report our protocol of daily oral acetylsalicylic acid (ASA) administration beginning within 48h after TSS for CD. **Methods:** A single institution database of adult patients undergoing TSS by the senior author was queried. All patients who met criteria for CD, had an adenoma staining for ACTH and received ASA 81 mg were included. ASA 81 mg was initiated within 48h of surgery and typically continued for six weeks. Patients wore bilateral lower extremity sequential compression devices during their entire hospitalization and were encouraged to ambulate after surgery. Patients were followed at one week and six weeks after surgery and an MRI was performed at three months after surgery. VTE studies were performed when clinically indicated; surveillance studies were not performed. **Results**: 49 consecutive patients were included. Patients were followed for a median of 76 (range 7 – 2,504) days. One patient (2%) with profound hypercortisolemia refractory to maximal medical, surgical and radiation therapy developed a VTE six months after surgery, resulting in mortality. No other patient had a postoperative VTE while on ASA. No patient had a postoperative intrasellar hemorrhage. Two patients (4%) had epistaxis, one (2%) requiring embolization on postoperative day 33 and one (2%) was treated with nasal packing. **Conclusions:** Early ASA within 48h after TSS for CD was well tolerated without hemorrhagic complications. The incidence and severity of epistaxis was not substantially increased. VTE were very rare under our protocol. Early ASA is not unsafe in patients undergoing TSS for CD and may help reduce the rate of VTE.

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The authors have no relevant relationships to report.

P17
Transcriptome Dynamics of *in vitro* Human Pituitary Tumor Primary Culture

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To gain insight into gene expression profile changes that occurred prior to/coincident with loss of hormone secretion during in vitro human pituitary tumor cultures, we compared the global transcriptiome landscape in serial passages from two human prolactinoma primary cultures. We obtained 27.1 million quality filtered reads per sample of which ~90% were exonic reads detecting an average of 16,000 genes. 3D principal component analysis identified 3 distinct clusters, with close similarity between cell passages 1-2, those beyond 4-5 and a stand-alone passage 3. Analysis of differential gene expression over time using DAVID and hierarchical clustering demonstrated that most gene expression changes occurred in the first 1-2 weeks in in vitro culture. At this stage, although the cells maintained robust PRL secretion, reduced activation of angiogenesis and growth signal pathways (PI-3K, MAPK pathways, cell adhesion, GTPase activity, cell proliferation and cell-cell junction assembly) was observed. In the following 1-2 weeks, the cell population maintained PRL secretion but exhibited continued loss of survival signals, with increased expression of extracellular matrix and surface adhesion molecules consistent with development of a fibroblastic phenotype that dominated later stage cultures. We propose that the molecular events underpinning loss of hormone production in primary pituitary tumor cultures represent transition from endocrine cells to pituitary specific fibroblastic cell likely selected by the in vitro culture conditions. Our data further reveal that underexpression of several GPCRs and resultant downregulation of the PKA pathway may lead to loss of hormone production in parallel with loss of cell survival signals. In summary, our study defines a temporal progressive transcriptome transition signature to explain loss of hormone secretion and morphological alterations observed during human pituitary tumor in vitro culture and may provide molecular targets to further optimize our culture methodology to attain "immortalized" hormone-producing human pituitary tumor cell-lines.

The authors have no relevant relationships to report.

P18
Transcriptome Profiling Identifies Distinct Features of Silent Corticotroph Adenomas

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Silent corticotroph adenomas (SCAs) present a clinically non-functioning pituitary adenomas (NFPAs) but ACTH-immunopositive staining without biochemical and clinical manifestation of hypercortisolism. SCAs usually present with mass-related symptoms and show aggressive course. We aimed to investigate the differential clinical and genetic signatures of SCAs compared with null cell adenomas (NCAs). We included 433 patients with clinically NFPAs who underwent transsphenoidal surgery at Seoul National University Hospital from May 2010 to April 2018. Among them, 69 (16%) adenomas showed positive immunostaining for ACTH (SCAs). Patients with SCAs were predominantly female (79.7%, $P<0.001$), had higher plasma ACTH and serum cortisol levels than those with non-SCAs. Age at diagnosis, body mass index, and tumor volume were not different between two groups. Patients with SCAs were at 3.3-fold higher risk for recurrence or progression compared with those with non-SCAs ($P=0.015$). In further analysis, using RNA sequencing, we examined the gene expression profile between 8 SCAs and 15 null cell adenomas (NCAs). Transcriptome analysis showed that the expression of 1,718 genes differed between SCAs and NCAs (fold change >2, $P<0.001$), of which 1,045 genes were up-regulated and 673 genes were down-regulated in SCAs. SCAs showed overrepresentation of genes involved in PI3K-Akt signaling pathway, cancer, focal adhesion, neuroactive ligand-receptor interaction, calcium signaling pathway, and endocytosis. Bioinformatic analysis identified *AVPR1B, SSTR1, T-PIT, WNT9A, EBF1,* and *EGFR* genes as being up-regulated and *EPHB6, EPHA8, SF-1, GATA3, GATA2,* and *FGFR* genes as being down-regulated. Our studies elucidated the distinct clinical and gene expression features of SCAs, which may help understanding the pathogenesis of SCAs. The study was approved by the Institutional Review Board of the Seoul National University Hospital.

The authors have no relevant relationships to report.

GROWTH HORMONE/ACROMEGALY

P19
Adjuvant Therapeutic Modalities in Acromegaly: Clinical Course and Factors Predicting Biochemical Controls

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Objective: Although surgical resection is the first line therapy for acromegaly, many patients do not achieve biochemical remission after surgery and require the adjuvant therapy including medical treatment, conventional radiotherapy, and gamma-knife surgery (GKS). There are few studies evaluating the efficacy of each adjuvant treatment. In this study, we investigated clinical course and disease control after initiation of adjuvant treatment. **Method:** We performed a single-center retrospective study including acromegalic patients treated with SSA at least for 6 months from January 1, 2005 to June 30, 2018. Age, gender, fasting GH, IGF-1 levels, 75g oral glucose tolerance tests and tumor size were measured before/after operation, medical treatments, or radiotherapy. The patients were considered biochemically controlled/cured if fasting mean GH levels were less than 2.5ng/ml or nadir GH after oral glucose loading was less than 1 ng/ml together with normalized IGF-1. **Result:** We analyzed 72 patients for median 62.9 months (40.0-111.5). The median age was 46 (37-53) years. The median duration of SSA use was 31.5 months (12.6-53.0). The median GH level was 30.5 (17.6-47.3) ng/ml, IGF-1 was 694.7 (600.0-862.8) ng/ml, initial tumor size was 24 (17.2-32.2) mm. Of 72 patients, 59 patients (81%) underwent surgical resection and 40 patients (55.6%) underwent GKS. Of the 40 patients who underwent GKS, 16 (40%) discontinued the medication after 26 (10.3-35.2) months. After treatment, 54 patients (75%) were biochemically controlled. Before initiation of SSA treatment, biochemically controlled group had significantly lower GH (3.63 vs 15.35ng/ml, p<0.001), IGF-1 (514.0 vs 641.9ng/ml, p=0.005), nadir GH after oral glucose loading (2.66 vs 7.9ng/ml, p<0.001) and basal glucose level (94.5 vs 104.5g/ml, p=0.098) than non-controlled group. **Conclusion:** In conclusion, basal GH level and presence of visible remnant tumor was correlated with biochemical response after adjuvant treatment. Appropriate adjuvant treatment should be decided according to the disease status of acromegalic patients.

The authors have no relevant relationships to report.

P20
Clinical Features and Tumor Size at Presentation in Acromegaly Patients by Age Group: A Large Single Center Retrospective Analysis

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Background: Acromegaly has an insidious onset of exaggerated soft tissue, bone growth, and various somatic symptoms. We investigated age-related differences in clinical presentation in adults. **Methods:** Retrospective analysis of an IRB-approved adult acromegaly repository was undertaken. Groups based on age at diagnosis were created; <30 years (Group1), 30-65 years (Group2), and >65 years (Group3). Statistical analysis with SPSS 25. **Results:** We reviewed 170 complete records; 31, 121, and 18 patients were in Groups 1, 2, and 3, respectively. Mean age at diagnosis was 47 years (±15); overall 55% were female (Group1;64%, Group2;53%, Group3;50%). Top presenting symptoms (>50%) in Group1 were headache, fatigue, acral enlargement, and weight gain; Group2 acral enlargement, headache, fatigue, arthralgia, and weight gain, and Group3 fatigue, arthralgia, and acral enlargement. Headache was reported less in Group3 ($p=0.02$) and arthralgia in Group1 ($p=0.02$). Menstrual disturbances ($p<0.01$), galactorrhea ($p=0.03$) and visual defects ($p<0.01$) were reported more in Group1. Most common findings in all groups were frontal bossing, hand enlargement and protruding jaw. Average delay in diagnosis was 3.7 (±3.6), 7.7 (±7.3), and 5.7 (±7.1) years in Groups1, 2 and 3 (Group1<Group2, $p=0.01$), respectively. There was no difference in baseline IGF-1 between groups. Mean pituitary adenoma size was 21.2 (±9.8), 15.8 (±9.0), and 12.4 (±7.4) mm in Groups 1, 2, and 3, $p=0.01$, respectively. **Discussion:** While acral enlargement and fatigue were the most common presenting symptoms across age groups, younger patients had less arthralgia, more menstrual disturbances, galactorrhea and visual defects, along with larger tumors. Patients >65 years had less headaches and no difference in either tumor size or baseline IGF-1 compared to 30-65 years. Delay in diagnosis across groups is lower than previously described. **Conclusion:** A wide variability in acromegaly presenting symptoms is revealed. Highlighted is the influence of age on clinical presentation.

MF is a consultant for Chiasma, Novartis, Ionis, Ipsen and Pfizer and her institution receives research support from Chiasma, Novartis, Ionis and Pfizer. The other authors have no relevant relationships to report. This abstract includes discussion of product(s) unlabeled (off-label) for use as approved by the FDA.

P21
Clinical Phenotypes of GNAS Gene Mutations in Acromegalic Patients

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Objective: Guanine nucleotide-binding protein, stimulating (GNAS) gene have been reported to be associated with GH secreting pituitary adenoma (approximately 40%). In this study, we investigated the prevalence of GNAS mutation in Korean acromegalic patients and assessed whether mutation status correlated with the biochemical or clinical characteristics. **Method:** Tumor genomic DNA was extracted from paraffin blocks obtained by surgery. GNAS gene mutation was analyzed with amplications of regions containing 2 hot-spot of activating somatic mutations in codons 201 and 227. Biochemical remission of acromegaly was defined as a normal serum IGF-1 level or nadir GH after oral glucose tolerance test (OGTT) was less than 1ng/ml. **Result:** We analyzed 126 patients. GNAS mutations were present in 75 of the 126 acromegalic patients (59.5%). Among the GNAS mutant patient, 61 subjects (81%) had mutation in codon 201. There was no difference in age distribution and Hardy classification according to presence of GNAS mutation. The mutation negative group was 76.5% female and the mutation positive group was 48.0% female ($p=0.006$). GNAS mutant group had higher prevalence of overall GH expression in immunohistochemical staining (98.7% vs. 92.2%, $p=0.015$). GNAS mutant patients are associated with higher IGF-1 level preoperatively (791.3 vs. 697.0ng/ml, $p=0.045$). Immediate postoperative basal GH (0.9 vs. 1.0ng/ml, $p=0.191$) and nadir GH (0.3 vs. 0.6ng/ml, $p=0.012$) in OGTT was lower in GNAS mutant patients. Surgical remission rates were significantly higher in GNAS mutant patients, evaluated both at immediately and at 6 months after operation (70.7% vs. 54.9%, $p=0.011$; 85.3% vs. 82.4%, $p=0.007$, respectively). **Conclusion:** GNAS mutation was more frequently found in Korean acromegalic patients. GNAS mutation positive tumors tended to have higher preoperative IGF-1 level, surgical remission rate and lower immediate postoperative nadir GH on OGTT. Identifying the GNAS mutation would be helpful in predicting patient's clinical features and prognosis.

The authors have no relevant relationships to disclose.

P22
Differentiated Thyroid Cancer in Acromegaly: Evolution in 4 Cases

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Introduction: Despite controlled studies, national registries and meta-analyzes, the relationship between acromegaly and cancer, which is continually revisited, remains controversial. In recent review, the standardized incidence ratio (SIR) ranged from 0.75 to 3.4 (Boguszewski and Ayuk, 2016). **Objective:** To report 4 cases of thyroid cancer diagnosed in acromegalic patients. **Methods:** The medical records of 79 acromegalic patients followed in a university-affiliated Center of Neuroendocrinology of southern Brazil, between 2013 and 2018, were reviewed. Of these, 13 cases were excluded because they had a follow-up of less than 1 year after the diagnosis of acromegaly. Four patients with thyroid cancer were diagnosed in this series, and consented to the publication of their data. **Case Reports: Case 1:** Female, diagnosis of acromegaly at age 60, with follicular variant of papillary microcarcinoma in 3 thyroid nodules, in two of them invading the capsule without overcoming it. **Case 2:** Female, diagnosis at age 49, papillary carcinoma with involvement of lymph nodes and pulmonary metastases. **Case 3:** Female, diagnosis at age 53, papillary carcinoma with invasion of perithyroid tissue. **Case 4:** Male, diagnosis at age 47, papillary carcinoma with lymph node metastases. In the last evaluation, the cervical lesion persisted only in the male patient, with no signs of disease in the other cases. **Conclusion:** In this report, the number of cases of thyroid cancer in relation to the total sample (4/66, 6%) is similar to that of other published series, and limited to differentiated carcinomas, with thyroid disease progression following the usual pattern. However, the findings reinforce the indication of continuous attention to the examination of the cervical region in acromegalic patients and ultrasound complementation according to the findings. This recommendation is especially valid in young patients with a family history of cancer, which are independent risk factors.

The authors have no relevant relationships to report.

P23
Echocardiographic Findings in Patients with Acromegaly; A Large Single-center Experience

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Background: Acromegaly is a rare disease with multiple cardiac abnormalities with cardiovascular morbidity representing a major mortality cause. A 2013 Acromegaly Consensus Group consensus statement recommends baseline echocardiography (ECHO) with optimal cardiac follow-up unknown. Here we describe prevalence of cardiac abnormalities on ECHO in acromegaly patients, at screening and follow-up. **Methods:** Retrospective review of 190 acromegaly confirmed patient records followed in the OHSU Northwest Pituitary Center; 2006-2018, was undertaken. Demographic, disease control data and ECHO (screening and follow-up if abnormal) were collected and analyzed with SPSS-25. **Results:** Almost 58% (110/190) of patients had undergone a screening ECHO; 54.5% were female and median age was 57.26 years (40.70–64.85). Time from first reported symptom to ECHO was 81.69 months (44.33–160.84) and from diagnosis to ECHO 6.58 months (1.02–44.43). Disease was controlled in 80%, and 13.6% had discordant IGF-1/GH. Screening ECHO data: left ventricular hypertrophy (LVH) 17.8%, LV dilation 3%, diastolic dysfunction (DD) 15.8%, and systolic dysfunction (SD) 7.9%. Median left ventricular ejection fraction (LVEF) was 62.6%, left atrium dilation 27%; valve dysfunction (VD) 87.3%, 14.6% (moderate-to-severe). Approximately 39% of patients had undergone a follow-up ECHO; median 36 months, 79.1% controlled disease, and 14% with discordant IGF-1/GH. Follow-up ECHO data: LVH 25.5%, DD 29.5%, and SD 9.1%. Moderate and severe LV dysfunction were 2.3% and 4.5%, respectively. VD 90.2%, moderate-to-severe 24.3%. No statistical significance was found in LVH, DD, SD, LVEF, and VD at follow-up or between controlled and uncontrolled patients. **Discussion:** Our data demonstrates that acromegalic cardiomyopathy is often diagnosed by ECHO and valve defects are highly prevalent compared with aged-normal population (89.4% vs 51%). In disease-controlled patients 17.6% (3/17) reversed DD, supporting reversibility potential. **Conclusion:** Though improvement may occur in isolated patients, there was no statistical difference in ECHO improvement over time at follow-up between controlled and uncontrolled acromegaly.

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P24

Ectopic Acromegaly and Small-cell Lung Cancer Sellar Metastasis – Importance of Radiological Features for an Accurate Diagnosis

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Radiological features are cumbersome in guiding studies in sellar tumors. Identification of normal pituitary tissue, sellar diaphragm anatomy and presence of stalk involvement may change differential diagnosis. We present a clinical vignette that highlights the importance of these issues. Fifty-seven-year-old woman with a past medical history of hypertension and smoking. She was referred due to bitemporal campimetric impairment. MRI showed 18 mm lesion with pars tuberalis involvement and heterogenous contrast uptake, suprasellar extension with chiasm abutted centrally and preserved sellar diaphragm. Normal pituitary tissue visible in the inferior and lateral aspect of the sella. Endocrinologic evaluation identified coarse facial features, polyuria but no other stigmata. Lab tests: prolactin 74.8 ng/mL, IGF-1 215 ng/mL (NV 36-200, Siemens), FSH 12.7 mUI/mL, TSH 3.41 uUI/mL, T4 7.6 ug/dL, cortisol 9.1 ug/dL, Na 143 mEq/L, Plasma Osmolality 316 mOsm/Kg, Urinary osmolality 493 mOsm/Kg. Due to elevated IGF-1, OGTT was performed showing a GH nadir of 1.87 ng/mL (Immulite 2000, Siemens). Due to atypical radiologic features and possible partial central diabetes insipidus, an ectopic source of GH/GHRH was suspected. CT scan was performed, revealing 3 large pulmonary lesions and multiple hilar lymph nodes; a transbronchial biopsy confirmed small-cell lung carcinoma. No plasma or immunohistochemistry of GHRH could be performed, but her sellar lesion was considered as a metastasis and the excess GH to an ectopic source. Systemic chemotherapy was initiated, with significant structural reduction of sellar tumor. No subsequent hormonal profiling was performed due to patient's preferences. This clinical vignette highlights the importance of radiologic and clinical features in guiding the study of sellar tumors, such as stalk involvement, normal pituitary tissue position within the sella, sellar diaphragm characteristics and neurohypophiseal function. Clinical suspicion of atypical lesions may lead to diagnostic procedures and change dramatically the prognosis in patients with pituitary tumors.

The authors have no relevant relationships to report.

P25

Effect of Growth Hormone Treatment on the Quality of Life of Patients with Growth Hormone Deficiency

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Introduction: Growth hormone deficiency (GHD) in adult life causes various metabolic and psychological disturbances. Most adult hypopituitary patients with GHD have compromised quality of life (QOL). Herein, we report the effect of GH replacement on the QOL of an adult GHD population assessed using 2 QOL subscales. **Patients and methods:** The subjects were 33 patients with adult-onset GHD who received GH replacement therapy for >1 year, including 24 men and 9 women, with a mean age of 47.8 years (range, 21–69 years). QOL was assessed using the 36-item Short Form (SF-36) and Adult Hypopituitarism Questionnaire (AHQ) at baseline and 12 months after GH replacement therapy initiation. **Results:** The AHQ results showed no significant correlations between the baseline values of the clinical/laboratory variables and QOL, but QOL tended to be poorer in the women. The mean changes in psychology/social domain ($p<0.01$), depression mode ($p<0.01$), limitation of social activity ($p<0.01$), vitality ($p<0.01$), and personal relations ($p<0.01$) were significantly increased after 12 months of GH therapy. The SF-36 results at baseline for physical component summary (PCS) and mental component summary (MCS) were below the standards for the healthy population (45.0: $p<0.01$ and 38.0: $p<0.01$, respectively). The mean change in MCS score was significantly increased after GH therapy but was still below the standard (40.1, $p<0.01$). Regarding physical function, the AHQ and SF-36 scores positively correlated. **Discussion:** The AHQ is a QOL evaluation method with high disease specificity and reflected accurately the change in QOL due to GH therapy. SF-36 is a comprehensive scale of QOL comparable that of generally healthy population. Although GH therapy for patients with GHD improves QOL, improvement to the level of healthy people has not been obtained in 1 year of treatment.

The authors have no relevant relationships to report.

P26
Glico-metabolic Effects of Pasireotide Treatment in Acromegaly

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Introduction: The prevalence of impaired glucose metabolism or diabetes mellitus in acromegaly varies between 19% and 56%. We aimed to evaluate glycol-metabolic assessment in acromegalic patients treated with Pasierotide and followed-up at our Pituitary Unit. **Material and Methods:** We conducted a retrospective study on our series of patients affected by acromegaly and treated with Pasireotide. The outcomes analyzed were fasting plasma glucose (FPG), hemoglobin A(1c) at baseline and at last follow-up. **Results:** 26 patients were enrolled. 17 patients (65.4%) reached the biochemical control of acromegaly. At baseline 5 patients were diabetics and 10 patients had impaired glucose tolerance (IGT). A worsening of the glycol- metabolic assessment occurred in 15 patients (53.6%). At the last follow-up, 15 patients were diabetics and 9 had IGT. At baseline, 12 patients did not require any treatment, 9 patients were on treatment with hypo-caloric hypo- glucidic diet, 2 patients with oral hypoglicemic and 4 patients with insulin. During follow-up, 6 patients did not require any treatment, 6 patients were on treatment with diet, 10 patients were on treatment with oral hypoglicemic and 4 patients with insulin. We did not find a correlation between metabolic assessment at follow-up and control disease. Similarly, the worsening of the glycaemic assessment at follow-up did not correlate with glycol-metabolic assessment at baseline without any significant difference between HbA1c at baseline of patients with worsening of glycemic status (median 5.6% IQR 0.75) and those without any worsening of this status (median 6.4% IQR 3). **Conclusion:** These data suggested that Pasireotide LAR had a direct effect on glycol-metabolic assessment, regardless of pre- treatment baseline glycemic status and of IGF-1 values.

The authors have no relevant relationships to report.

P27
Glyco-metabolic Effects of Pegvisomant Treatment in Acromegaly

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Introduction: Hyperglycemia is a common feature associated with state of GH hypersecretion. The role of Pegvisomant (PEG) in glyco-metabolic assessment in acromegaly is still subject of investigation. **Material and Methods:** We conducted a retrospective study on our series of patients affected by acromegaly and treated with PEG. The outcomes analyzed were fasting plasma glucose (FPG), hemoglobin A (HbA1c) at baseline and at last follow-up. **Results:** We have analyzed a cohort of 44 patients treated with PEG, of which 30 in association with SSA. At last follow-up, 32 patients reached disease control (73%). A worsening of the glyco-metabolic assessment occurred in 19 patients (43.2%). At baseline, 8 patients were diabetics and 13 patients had impaired glucose tolerance (IGT). At last follow-up 12 patients were diabetics and 11 had IGT. HbA1c at baseline is related to Hba1c at follow-up (P<0.001 r:0.6). At baseline, 21 patients did not require any treatment, 11 patients were on treatment with hypoglucidic diet, 10 patients with oral hypoglycemic and 2 patients with insulin. During follow-up, 19 patients did not require any treatment, 8 patients were on treatment with diet, 12 patients with oral hypoglicemic and 5 patients with insulin. Variations of Hba1c values is similar in patients treated only with PEG and in patients treated with PEG and SSA (p=0.9). Patients with worsening of glycaemic status had higher HbA1c at baseline (median 6.7%, IQR: 1.3) as compared to patients without worsening of metabolic assessment (median 5.7%, IQR: 1.4). Similarly, patients who required an increase in antidiabetic therapy had higher HbA1c at baseline (median 6.6%, IQR 1.1) as compared to other patients (median 5.7% IQR 1.4). **Conclusion:** Our data suggested that the worsening of glycemic status during follow-up seems to be related to pre-treatment glyco-metabolic assessment rather that to treatment for acromegaly and disease control.

The authors have no relevant relationships to report.

P28

Impact of Octreotide Treatment in Serum Concentrations of Lipossoluble Vitamins A, D, E in a Cohort of Acromegalic Patients

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Background: Somatostatin analogues can induce a malabsorptive profile related to its effects reducing the secretion of pancreatic enzymes and bile salts for overriding the absorption of fat-soluble vitamins. There is a lack of data on the impact of treatment and hormonal control in lipossoluble vitamins in patients with acromegaly. **Objective**: To evaluate vitamins A, D, and E before and after 3 and 12 months of treatment with octreotide and its association with disease control in acromegalic patients. **Methods**: A cross sectional, case series study, composed of 35 patients, submitted to a washout of octreotide for 90 days before the study. Blood samples were collected before, 90 and 360 days after reintroduction of Octreotide LAR, and serum levels of calcium, GH, IGF-1, PTH, Vitamins A, 25 OH D, E, and the tests D-xylose and fecal fat study were performed. A dietary survey was conducted to determine the profile of intake of the main food sources of fat-soluble vitamins. Statistical analysis was performed using MedCalc 12.3.0. Students' t test was used, $p < 0.05$, SPSS 17.0. The study was approved by the local Ethical Committee. **Results:** The cohort was homogeneous in age, sex, time since diagnosis, previous use of Octreotide and washout. A reduction in serum GH and IGF-1 and Vitamin D after exposure Octreotide was observed ($p < 0.05$) but not on Vitamins A and E. The intake of dietary sources of fat-soluble vitamins was lower among the patients, but vitamin A and E levels did not reflect hypovitaminosis. There was no correlation between the activity of acromegaly, D-xylose and fat-soluble vitamins. **Conclusion:** There was an impact on the malabsorption of octreotide, reflected by reduction on the concentration of vitamin D. Long-term studies may be necessary to clarify the relationship between drug treatment and levels of vitamins, and its role on comorbidities.

The authors have no relevant relationships to report.

P29

Long-term Effects of Growth Hormone Replacement Therapy in Childhood-onset Craniopharyngioma: Results of the German Craniopharyngioma Registry (HIT-Endo)

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Objective: Quality of survival, prognosis and long-term outcome are often severely impaired in childhood-onset craniopharyngioma patients (CP). Identification of risk factors for sequelae such as growth hormone (GH) deficiency is important for appropriate treatment and rehabilitation. **Design**: In a cross-sectional study, 79 CP recruited in HIT-Endo before 2000 were analyzed according to GH substitution: a. CP never GH-treated (noGH); b. CP GH-treated only during childhood (pedGH); c. CP under GH, initiated at adulthood (adultGH); d. CP under GH during childhood and continued during adulthood (contGH). **Methods:** Progression-free (PFS) and overall survival (OS), height, body mass index (BMI), psychosocial and neuropsychological status (EORTC QLQ-C30, MFI-20). **Results:** OS and PFS rates were similar in all subgroups. ContGH and pedGH CP presented with increases in height ($p=0.002$; $p=0.0001$) during long-term follow-up when compared with baseline. In all subgroups except for pedGH, increases in BMI were observed when compared with BMI at diagnosis. For emotional functionality and physical fatigue, adultGH CP showed worse ($p=0.037$; $p=0.034$) response (mean: 61.4%; 12.5%) when compared with pedGH CP (mean: 83.5%; 7.7%). Observed differences were not related to irradiation and hypothalamic involvement. In terms of psychosocial status, no differences were observed between subgroups. **Conclusions:** We conclude that GH substitution was safe with regard to risk of tumor progression/relapse in CP. Growth was improved by GH, whereas the development of obesity was not influenced by GH substitution. However, early initiation of GH substitution after CP diagnosis might have beneficial effects on weight development and neuropsychological outcome.

The authors have no relevant relationships to report.

P30

Monitoring of Therapy Adherence in Adults with Growth Hormone Deficiency: Preliminary Monocentric Data with Easypod™ Connect

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Objective: Non-compliance to recombinant human growth hormone (r-hGH) therapy in adult growth hormone deficiency (aGHD) is a major concern for endocrinologist, as it affects significantly efficacy outcomes. This twelve-month observational study was aimed to assess adherence in GHD patients treated with r-hGH administered via Easypod™ (Merck Serono Spa, Italy) an electronic, fully automated injection device designed to track the time, date and dose administered. **Methods:** 65 patients receiving r-hGH therapy were included in the study and 32 completed the study. The primary endpoint, adherence to treatment, was calculated as the proportion of injections correctly administered during the observational period out of the expected total number of injections. Adherence, tracked by the Easypod™, was evaluated at months 6 (V1) and 12 (V2) after baseline (V0). As secondary end-point, serum IGF-1 levels were also determined. The study protocol was approved by a local Institutional Board. **Results:** The Easypod™ data showed a median adherence of 80% throughout the period V0-V2. Females are more compliant than males. Adherence levels are correlated to IGF-1 ones. **Conclusions:** Adherence is connected with therapy's efficacy in aGHD. The injection-recording system and other characteristics of Easypod™ could enhance the ability of physicians to monitor adherence to r-hGH treatment, identifying non-compliant patients, thus enabling physicians to modify their management to maximize the benefits of the treatment.

The authors have no relevant relationships to report.

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Mortality Among Patients with Acromegaly on Pegvisomant Therapy – An Acrostudy Analysis

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Acromegaly is associated with increased mortality risk, which has been attributed to cardiovascular, cerebrovascular and malignant disorders. Effective treatment of acromegaly mitigates excess mortality. However, the relative importance of IGF-I and GH levels as predictors of mortality in this population is a subject of ongoing debate. The study aims were to characterize morbidity and mortality in patients with acromegaly on pegvisomant therapy. Searches were conducted among patients that were participating in ACROSTUDY, a global observational outcomes study of patients with acromegaly treated with pegvisomant. Kaplan-Meier analyses and regression techniques were used to examine survival in patients with acromegaly and identify predictors of mortality in this population. Searches identified 2221 patients, including 1092 women and 1129 men, whose age at study entry (mean ± SD) was 51.0 ± 14.3 yr and BMI was 29.6 ± 5.3 kg/m^2. There were 621 patients (28%) with hypopituitarism; 410 patients were smokers. Baseline IGF-I levels before starting pegvisomant therapy were 514 ± 313 ng/ml. Patients were treated with pegvisomant at a dose of 13.7 ± 7.0 mg/daily and were followed for a median interval of 1402 days (range: 1 to 4773). There were 87 deaths during the observation period, mostly due to cardiovascular disease or malignancy. Predictors of mortality included older age at study entry (P<0.0001), higher BMI (P=0.0044), smoking (P<0.0001), hypopituitarism (P<0.0001), and the presence at study entry of hypertension (P<0.0001), cardiovascular disease (P<0.0001), cerebrovascular disease (P<0.0001), diabetes mellitus (P<0.0001), dyslipidemia (P<0.0001), sleep apnea (P<0.0001), malignancy (P<0.0001), and longer duration of acromegaly (P<0.0001). On regression analysis, older age at study entry, higher BMI, hypopituitarism and the presence at study entry of hypertension, cardiovascular disease, diabetes mellitus, sleep apnea and malignancy were associated with higher mortality risk. On Kaplan-Meier analysis, patients with acromegaly and cardiovascular disease at study entry had higher mortality than those without cardiovascular disease at baseline (P<0.0001). Data on mortality in relation to IGF-I normalization will be presented at the meeting. In summary, patients with acromegaly are at risk of mortality, mainly from cardiovascular and malignant disease. Older age, higher adiposity, hypopituitarism, hypertension, diabetes mellitus, cardiovascular disease, sleep apnea and malignancy are associated with higher mortality risk in this population.

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P32

Pre-surgical Treatment with Somatostatin Receptor Ligands May Worsen Glucose Metabolism in Patients with Acromegaly

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Purpose: To evaluate the serum glucose levels of patients with acromegaly undergoing transsphenoidal surgery, pre-treated or not with somatostatin receptor ligands (SRL). **Patients and Methods:** We retrospectively studied 181 patients attending the Unit of Neurosurgery of our Hospital prior to transsphenoidal surgery. All patients had a diagnosis of acromegaly (nadir GH during OGTT >0.4 ng/mL; and IGF-I above age-standardized UNL); diagnosis of diabetes (DM) and impaired fasting glucose (IFG) was performed on fasting blood glucose (FBG) according to the American Diabetes Association guidelines; all parameters of the pituitary axes were determined. Data are presented as mean±SD; normally distributed continuous variables were analyzed by Student-t test; categorical data by chi-squared test. **Results:** 97 (54%) patients with acromegaly underwent pre-surgical treatment with SRL; SRL treated and non-treated patients had similar age (53±11 vs. 51±12 years, respectively; p=NS) and gender (M/F: 51/46 vs. 43/41, respectively; p=NS). As expected, FBG was positively correlated with age (r=0.18, p<0.02) and IGF-1 (r=0.24, p<0.002). We found no difference in FBG between SRL treated vs. non-treated patients (106±24 vs.104±44 mg/dl, respectively; p=NS). However, we found increased proportions of IFG and DM patients in SRL treated vs. non-treated patients (euglycemic: 45%, IFG: 42%, DM: 13% vs. euglycemic: 70%, IFG: 22%, DM: 8%, respectively; p=0.006). Furthermore, in multiple logistic regression analysis, SRL treatment independently increased the odds ratio of IFG and DM (OR 4.7; 95%CI 2.1-10.3). **Conclusions:** Our findings show that the proportion of patients with acromegaly undergoing surgery with glycemic levels in the range of DM, is modest. Among the patients with high glucose levels, the risk factors are advanced age, IGF-1 levels, and pre-treatment with SRL. We conclude that the choice of pre-treating with SRL patients with high glucose levels at baseline should be carefully balanced against possible advantages.

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Prevalence of Vertebral Fractures in Patients with Acromegaly - Large Single Center Retrospective Study

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Introduction: It was shown recently that patients with acromegaly have higher risk for vertebral fractures (VF) compared to the general population. **Methods:** A cross-sectional retrospective record review of VF and bone mass density; BMD (IRB approved, OHSU Pituitary Center; 2006-2018) in 190 acromegaly patients. VF were assessed through spinal x-rays (from 2010 per international consensus guidelines) and BMD was evaluated by DEXA. SPSS-25 was used for statistical analysis. **Results:** From 134 patients (45.7% female) with spinal x-rays, 25.37% had fractures (78 total fractures). Mean age was 50.05 years (±15.30), at time of VF diagnosis. 18 patients had >1 fracture; most were thoracic spine (76.47%). VF were predominantly mild (Genant-1) 64.7%, moderate (Genant-2) 14.7%, severe (Genant-3) 2.9%. 14.7% had minimal vertebral wedging comprising <20% anterior height loss (Genant-0). 104 patients had DEXA scans: mean age was 45.79 years (±14.17); 35.57% and 5.76% had osteopenia and osteoporosis, respectively. 93 patients had both screening DEXA and x-rays. There was a weak, but statistically significant correlation between IGF-1 at time of acromegaly diagnosis and VF presence (rs=0.29, p=0.002). There was no correlation between osteoporosis/osteopenia on DEXA or VF on x-rays and any of the following: age at time of diagnosis, medical or radiation treatment of acromegaly, serum calcium and vitamin D, presence of hypogonadism, hypothyroidism, diabetes mellitus type 2, or adrenal insufficiency. There was no correlation between osteoporosis on bone density and VF on x-rays. **Conclusion:** In this study, VF, albeit the majority mild, were observed in approximately ⅓ of acromegaly patients. This prevalence is almost double that of the general population, despite acromegaly patients with VF being younger. Bone density is not a reliable marker for risk of fractures in acromegaly patients. Increased awareness of bone disease and individualized patient treatment are required, as no predictive factors have been identified in acromegaly.

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P34
Quality of Life, Growth, and Hypothalamic Lesions in Childhood-onset Craniopharyngioma

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Objectives: Quality of life (QoL) after childhood-onset craniopharyngioma (CP) is frequently impaired by tumour and/or treatment-related factors such as endocrine deficits and hypothalamic involvement (HI). **Methods:** We prospectively analyzed parental and self-assessment of CP patient QoL at 3 mo, 1 and 3 yrs after CP diagnosis related to growth hormone (GH) substitution and HI. Forty-seven of 194 CP patients recruited 2007-2015 fulfilled the inclusion criteria: 1) histological CP diagnosis, 2) age at diagnosis 6-18 yrs; 3) availability of QoL data one and three yrs after diagnosis. QoL was assessed using the Pediatric Quality of Life (PEDQOL) questionnaire. **Results:** Parents estimated QoL of their children worse than patients did themselves for the PEDQOL domains emotional stability (3 mo, $p<0.05$; one yr, $p<0.001$) and social function/friends (one yr, $p<0.01$; 3 yrs, $p<0.05$). HI was associated with lower self-assessed QoL 3 mo after diagnosis (body image, $p<0.01$; social function/friends, $p<0.01$). The negative impact of HI on QoL was greater for parental assessed QoL at all time points. GH substitution had no relevant effect on short-term weight and height development. CP patients, GH-treated at 3 yrs follow-up, presented at baseline (1 yr after diagnosis, before GH substitution) with reduced self-assessed QoL for the PEDQOL domains autonomy ($p<0.05$), cognition ($p<0.01$), physical function ($p<0.05$), and social function/friends ($p<0.01$), when compared with GH non-treated CP patients. QoL stabilized during 1-3 yrs of follow-up in GH treated patients, whereas non GH-treated patients experienced decreases in QoL for the PEDQOL domains physical function and social function/friends. **Conclusions:** Parents assess QoL in CP survivors worse than their children. As HI is a major risk factor for reduced QoL, treatment strategies in CP should aim at prevention of (further) hypothalamic damage. GH substitution should be considered as an effective option to ameliorate imminent impairments of QoL after CP.

The authors have no relevant relationships to report.

P35
Remission Rates in Patients with Acromegaly Using Multi-modality Therapies: Real-life Outcomes from a Pituitary Center and Changes Over Time

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Background: Remission rate for acromegaly after transsphenoidal surgery (TSS) and/or medical therapy varies widely depending on the study. Few studies have evaluated the long-term remission rate in response to multi-modality therapies. With the advance of new medical therapies over the last decades, we sought to determine the real-life, long-term, multi-modality remission rate and changes in therapies over time. **Subjects and Methods:** This was an institutional review board-approved longitudinal study in a Clinical Research Center. Records of patients with biochemically and/or pathologically confirmed acromegaly, seen between 1980 and 2018 at a single Pituitary Center were reviewed (N= 238) and included if they underwent TSS, and had at least one IGF-1 level available at $\geq$ 6 months after surgery (N=172, 103 Female). T- test and Mann–Whitney U test were used to compare continuous data between time periods. Categorical variables were compared using the $\chi 2$ test or Fisher's exact test. **Results**: At diagnosis, age was 43.0 ±15.1 years (mean ± SD), BMI was 28.8 ± 6.2 kg/m^2; serum IGF-I index (IGF-1 level/ highest normal range) was 2.5 ± 1.2; 144 (83.7%) had macroadenomas. At a median follow-up of 7.92 [11.8] years (median [IQR]) post TSS; 145/172 (84.3%) achieved biochemical remission. Among those with TSS after 2003, radiation therapy (RT) was less common vs. those who underwent TSS before 2003, (26/115 [22.6%] vs. 28/57 [49.1%]), P <0.001). The prevalence of medical therapy did not differ [61/115 (53.0%) vs. 29/57 (50.9%), P= 0.87], but the interval to first normal IGF-1 level was less in patients who had TSS after vs. before 2003: 5 [10.0] vs. 35 [54.5] months, P <0.001. **Conclusions**: The vast majority of patients who underwent TSS for acromegaly had normal IGF-1 levels in long-term follow up with multi-modality therapy. RT and time to normalization of IGF-1 decreased over time.

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P36

Screening for Comorbidities in Acromegaly: A Quality Improvement Project at a Tertiary Pituitary Center

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Background: Acromegaly is associated with serious complications and increased mortality; evaluation for hypertension, diabetes mellitus, cardiovascular disease with ECHO, lipid panel, sleep apnea, colon neoplasia, and recently, also vertebral fractures with X-rays, is recommended at diagnosis. **Methods:** Assess appropriate comorbidity screening in acromegaly patients followed at our Pituitary Center 2006-2018: both with new diagnosis and those previously treated who transferred their care to OHSU (2006 electronic medical record; EMR instituted) via retrospective analysis of an institutional IRB-approved acromegaly patients' database. **Results:** One-hundred and eight EMRs were reviewed; 53% female; mean age at diagnosis 47 (±16 years); mean follow-up 2.9 (±3.3 years).

		Year of Acromegaly Diagnosis		
		Before 2006 (n=16)	2006–2011 (n=48)	2012–6/30/2018 (n=44)
Percentage screening during 1st year of diagnosis	Polysomnography	0%	5/36(14%)	6/32(19%)
	ECHO	0%	13/45(29%)	20/40(50%)
	Vertebral X-rays	0%	12/48(25%)	26/44(59%)
	Colonoscopy	0%	3/38(8%)	7/29(24%)
	HbA1C	0%	11/37(30%)	19/32(59%)
	Lipids	1/16(0%)	8/42(19%)	7/31(37%)

Overall screening percentage rates (any year of acromegaly diagnosis) during 2006-2011 and 2012-2017 were: polysomnography 17.5% and 10%, ECHO 43% and 41%, X-rays 39% and 58% (p=0.032), colonoscopy 17.5% and 28%, HbA1C 39.5% and 53%, and lipids 30% and 29%, respectively. Blood pressure was measured at every visit. Thyroid was palpated at initial visit and periodically thereafter. **Discussion:** At our tertiary Pituitary Center, many patients are closely followed initially after diagnosis/surgery and then returned to local care. Patients diagnosed before 2006 had a significant delay in screening. Those diagnosed thereafter had progressively shorter delay in screening, with more than half screened within the 1st year by ECHO, X-ray, and HbA1C. Screening rates for newly diagnosed and patients who had not had appropriate screening prior to their first visit with us increased significantly ($p<0.05$) for X-rays and non-significantly ($p>0.05$) for colonoscopy and HbA1C. Percent screening with polysomnography, colonoscopy, and lipids remains low. **Conclusion:** Despite EMR use, screening for some comorbidities is either not performed or not available in almost 50% of patients. This necessitates development of strategies to ensure timely completion of appropriate screening tests for all acromegaly patients and checklists before scheduling appointments.

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P37
Successful Treatment with Octreotide and Cabergoline in a Girl with Mc Cune Albright Syndrome (MAS) and Growth Hormone (GH) excess: Adult Height According to Genetic Target After 12.6 Years Follow Up

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Background: MAS, is a rare genetic disease clinically defined by bone fibrous dysplasia, café au lait skin spots and at least one hyperfunction endocrinopathy. GH excess has been described in 20% of patients usually accompanied by hyperprolactinemia (80 %). GH hypersecretion is reported to be associated with a high risk of craniofacial and systemic morbidity. Medical therapy is first line treatment and includes somatostatin analogs, GH receptor antagonist, and dopamine agonists. Treatment goal is to maintain IGF1 Z-score between -2 + 1 SDS and growth velocity according to Tanner stage, sex and age. **Clinical Case:** 15 year old girl, without personal and family relevant history, was sent for endocrinological evaluation at 2.72 years, because of tall stature (height +2.57 SDS), high growth velocity (12cm/y) and advanced bone age (4y). Physical exam showed no pubertal signs and a large café au lait skin spot characteristic of MAS. GH excess was diagnosed by the lack of GH inhibition on OGTT (nadir GH 13.4ng/ml) and IGF1 + 3.32 SDS. No other endocrinopathies were detected. Pituitary MRI was normal. Octreotide LAR was started at a dose of 0.15mg/kg every 28 days. After 1 year follow-up cabergoline was added at 1mg/week, due to the lack of full response on auxiological (growth velocity 9cm/y) and analitical parameters (IGF1+1.25 SDS; GH 5ng/ml; PRL 39pg/ml). Under combined treatment all parameters normalized, and remained according to sex, age and Tanner stage. Menarche was presented at normal age (12.56 y) and reached adult height (169.3cm) according to genetic target (169.9cm). During 12.6 years of follow-up, there were no other endocrinopathies diagnosed, MRI remained normal and no adverse events were found. **Conclusions:** This clinical case emphasize the effectiveness and safety of an early combined treatment with somatostatin analogs and cabergoline in a girl with MAS and GH excess.

The authors have no relevant relationships to report.

MISCELLANEOUS

P38
A Case of a Pituitary Stone

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Objective: To describe a case of pituitary stone, a dense calcification of the sella turcica, that arises de novo or secondary to pathological intrasellar lesions. **Case**: A 70-year-old woman was evaluated after an incidental pituitary lesion was found on neuroimaging. Computed-tomography revealed a prominent pituitary gland with focal calcification in the anterior sella. Magnetic resonance imaging revealed a focal area of reduced enhancement in the left sella with complete loss of signal seen within the lesion, suggestive of a pituitary calcification. Chart review revealed that the intrasellar calcification was identified on neuroimaging ten years earlier, without change in size or morphology. The patient denied a history of pituitary disease or tuberculosis. She denied changes in hand or shoe size, weight, skin, or vision. A pituitary panel was unremarkable. Given the chronic stability of the lesion and absence of neurologic or endocrinologic abnormalities, periodic MRI surveillance was recommended. **Discussion**: Intrasellar calcifications have a broad differential, and commonly represent pituitary adenomas. The de novo pituitary stone is rare. Pituitary adenoma calcification can be observed in secretory and non-secretory tumors, most frequently documented in prolactinomas and GH-secreting tumors. Their management often entails surgical resection. The management of a pituitary stone without an underlying pathology depends on the associated neurological and hormonal abnormalities. The pathogenesis of pituitary calcification is incompletely understood, though it is believed to result from local effects of tumors, inflammation, hemorrhage, amyloid deposits, or infections. The mechanism of the de novo pituitary stone is unknown. **Conclusion**: Pituitary stone, a dense, focal calcification of the sella, is a rare yet well-documented radiographic entity. It often results from intrasellar pathology, though rarely occurs without an obvious etiology. Given the chronicity of the lesion, absence of sellar enlargement, neurological or endocrine abnormalities, we conclude that our patient has a de novo pituitary stone.

The authors have no relevant relationships to disclose.

P39
Acute Sheehan's Syndrome Presenting with Hyponatremia Followed by a Spontaneous Pregnancy: Case Report

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Background: Acute Sheehan syndrome (SS) is rare, as well as hyponatremia as its initial manifestation. Spontaneous pregnancy in SS is unusual. We describe a case of SS that presented with acute hyponatremia and a spontaneous pregnancy. **Case:** A 34-year-old female developed blood loss during delivery, which required transfusion of blood. On day 7 postpartum she presented with headaches, lethargy and difficulty in breastfeeding. Workup showed hyponatremia (118 mEq/l), secondary hypothyroidism and low prolactin levels. MRI showed pituitary necrosis. She was treated with NaCl, hydrocortisone (cortisol results were not available), and levothyroxine. Lab work 6 weeks after discharge showed low IGF-1 and 8 AM cortisol, and normal FT4, LH, FSH and PRL levels. She was able to partially breastfeed till 4 months postpartum. Regular menstrual cycles started 3 months later. She became spontaneously pregnant 1 year later. **Discussion:** SS is rarely diagnosed acutely; it is generally detected several years postpartum. Hyponatremia is an unusual initial symptom of acute SS. It may be due to diminished free water clearance by hypothyroidism and adrenal insufficiency. Moreover, glucocorticoid deficit may enhance inappropriate secretion of vasopressin. Gonadotropin function was not affected or restored. She was able to breastfeed, maybe due to partial lactotroph deficiency or recovered function. Recovery of hormonal function is rare but has been reported in the first year postpartum in acute SS. Pituitary necrosis is often incomplete, which may explain preservation of axes. To our knowledge no cases of spontaneous pregnancies after acute SS have been reported. In our case gonadotropin was functional, so pregnancy was a possibility. **Conclusion:** Acute SS should be considered in the evaluation of postpartum patients with suggestive symptoms. Physicians should be aware that hyponatremia could be an initial manifestation of SS, which requires a high index of suspicion for diagnosis. Spontaneous pregnancy can occur after acute SS.

The authors have no relevant relationships to report.

P40
Cell Cycle and DNA Damage Control Mechanisms in Nonfunctioning Pituitary Adenomas

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Molecular mechanisms underlying nonfunctioning pituitary adenoma (NFA) formation are largely unknown. In this study, we aimed to investigate the relationship between NFA and functional pituitary adenomas and expression of mRNA and proteins involved in cell cycle and DNA damage control mechanisms. We analyzed pATM-S198, pRb-S608, Rb, pE2F1-S364, p16, E2F1, p73, Cyclin D1 and CHEK2 protein and mRNA expression by immunohistochemistry (twenty acromegaly, twenty Cushing's disease, twenty-seven NFA patients) and qRT-PCR (seven acromegaly seven Cushing's disease, seven NFA patients). The study was approved by the Clinical Research Ethics Committee of Cerrahpaşa Medical School, Istanbul University, date and number 06/04/2017-133989. Categorical data between groups were compared using the $\chi 2$ and Fisher's exact test. Data were assessed for distributional normality, and for normally distributed data, parametric One-way ANOVA analysis was done and non-parametric Kruskal-Wallis test was used for data that were not normally distributed. There was no difference between all tumor types for pATM-S1981 and pRb-S608 expression intensity ($p > 0.05$). Rb protein expression was significantly higher in the NFA group compared to acromegaly ($p=0.038$), and pE2F1-S364 protein expression in Cushing group was significantly lower than NFA and acromegaly groups ($p=0.049$, $p=0.059$ respectively). In contrast, expression of p16 protein was significantly higher in the Cushing than in the NFA group ($p=0.038$). In contrast, E2F1 protein expression was significantly higher in NFA compared to the Cushing group ($p=0.006$). p73 protein expression in acromegaly was significantly higher ($p=0.013$) than in the Cushing group. Our observed selective tumor-specific association between E2F1, pE2F1-S364, CHEK2 and p73 mRNA and protein expression levels indicate their involvement in pituitary adenoma formation in NFA, Cushing's disease and acromegaly patients. The results of this study will help elucidate the molecular mechanisms underlying pathogenesis of pituitary adenomas and will contribute to the development of new approaches in the treatment and prevention of disease.

The authors have no relevant relationships to disclose.

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Cellular Heterogeneity in Pituitary Adenomas: A Review of Immunohistochemical Staining of Transcription Factors in Adenomas Received Over an 8-month Period

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Introduction: With the possible exception of 'double adenomas', pituitary adenomas (PA) are considered to be purely clonal neoplasms. The 2017 WHO Classification of Endocrine Neoplasms recommends routine usage of lineage-specific transcription factors (TF) for more accurate categorization of PA. We reviewed the immunohistochemical (IHC) staining patterns of TF applied to PA since the introduction of our first TF, SF-1. **Method:** Thirty-eight cases collected from May-December 2017 were reviewed (27 non-functioning adenomas and 11 functioning adenomas (6 GH; 1 PRL, 4 ACTH)). IHC for SF-1 (38 cases), PIT-1 (29 cases), and T-PIT (14 cases) was performed. In addition, IHC for SOX2, a pituitary stem cell marker, was applied in 31 adenomas. **Results:** Thirty-four PA were subclassified as follows:

PA subtype	Number of cases (%)
Gonadotroph	21 (55%)
Somatotroph	3 (7.9%)
Plurihormonal PIT1 positive pituitary adenoma	3 (7.9%)
ACTH-producing pituitary adenoma (prior to introduction of TPIT antibody)	3 (7.9%)
Corticotroph adenoma (TPIT antibody in use)	2 (5.3%)
Lactotroph adenoma	1 (2.6%)
Null cell adenoma	1 (2.6%)
Other/ heterogeneous staining	4 (10.5%)

Four PA (10.5%), however, demonstrated expression patterns consistent with a mixture of cell types of different lineages (SF1+/ACTH+, SF-1+/PIT1+, SF-1+/PIT1+/TPIT+). Typically, one cell type predominated within the adenoma. Furthermore, of 31 adenomas immunostained against SOX2, 18 (58.1%) adenomas harbored a variable number of SOX2+ cells, suggesting a less differentiated ('stem-like') component to these tumors. Interestingly, one null cell adenoma (SF-1-/PIT1-/TPIT-) was diffusely SOX2 positive. **Conclusion:** Given the challenges with hormonal IHC, the application of lineage-specific TF enables the accurate classification of PA. Surprisingly, however, this has identified cellular heterogeneity within a subset of adenomas. Recognition of this heterogeneity and correlation to clinical outcomes may provide additional insights into their biological behavior.

The authors have no relevant relationships to report.

P42
Collision Sellar Lesions: Coexistence of Pituitary Adenoma and Rathke Cleft Cyst

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Introduction: Collision lesions represent the combination of distinct histopathological lesions. Rathke cleft cyst (RCC) can coexist in about 1% of pituitary adenoma (PA) cases. Although they may be coincidental findings, their origin has still not been fully elucidated. **Objective:** Report our single-center experience of coexistent PA and RCC. **Methods:** Retrospective study of histopathological reports from patients operated for PA from 2013-2018 in a neurosurgery reference center. Patients who also presented with RCC were included. Clinical and biochemical data were collected from medical files. MRI and histopathological data were reviewed. **Results:** Among 554 PA, five patients (three females) had coexistent PA and RCC. At diagnosis, patients presented at median age of 60 years (33-78) with, at least, one pituitary dysfunction, and visual field loss and/or headache. Preoperatively, patients were suspected of harboring cystic non-functioning PA (NFPA) or RCC in four cases or craniopharyngioma in one case due to marked hypointense signal in T2W that could correspond to calcifications. MRI scans were unable to distinguish both sellar lesions. All patients were submitted to transsphenoidal surgery. During surgery, one patient (case1) was suspected of having craniopharyngioma due to the presence of macroscopic cholesterol crystals, not seen on MRI. The definitive diagnosis was made by histopathology analysis where a neoplastic proliferation of cells was seen next to cuboidal ciliated epithelium positive for epithelial membrane antigen and negative for chromogranin. NFPA of gonadotrophic origin were present in all cases, which is the commonest PA subtype in surgical series. In case1, RCC ruptured causing a granulomatous reaction with cholesterol clefts and foreign body giant cell reaction. **Conclusion:** Collision lesions should be considered in the differential diagnosis of solid-cystic and cystic sellar lesions. However, this diagnosis can only usually be made during histological study. The correct diagnosis of the pituitary lesion is important for proper post-operative management.

The authors have no relevant relationships to report.

P43
Low Concordance Between Surgical and Radiological Assessment of Degree of Resection and Treatment-related Hypothalamic Damage – Results of KRANIOPHARYNGEOM 2007

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Background: Assessment of presurgical hypothalamic involvement (psHI) and treatment-related hypothalamic damage (trHD) is relevant for the decision on risk-adapted treatment and rehabilitation strategies in craniopharyngioma. **Patients and Methods**: 129 surgical reports of childhood-onset craniopharyngioma patients recruited 2007-2014 in KRANIOPHARYNGEOM 2007 were analyzed. Data on psHI were available based on surgeon's (63%), reference neuroradiologist's (95%), and local radiologist's (23%) assessment. The surgical degree of resection (DoR) was assessed by neurosurgeon (95%), reference neuroradiologist (73%), and local radiologist (61%). TrHD was assessed by neurosurgeon (33%), by reference neuroradiologist (95%), and by local radiologist (2%). Neurosurgical center size was categorized based on patient load. **Results:** Surgical assessments on psHI (n=78), DoR (n=89) and trHD (n=42) as documented in surgical reports could be compared with the assessment of respective parameters by reference neuroradiologist. Differences with regard to DoR (p=0.0001) and trHD (p<0.0001) were detectable between surgeon's and reference neuroradiologist's assessment, whereas psHI was assessed similarly. Concordance for DoR and trHD was observed in 48% and 62%, respectively. Surgeons estimated a higher rate of complete resections and a lower rate of trHD. Neuroradiological reference assessment of trHD had higher predictive value for hypothalamic sequelae then surgical assessment. Observed differences were not related to neurosurgical center size. **Conclusions:** Observed differences between surgical and neuroradiological estimation of risk factors in craniopharyngioma support the necessity of neuroradiological reference review to assure standards of quality. This could be established by central internet-based neuroradiological review in KRANIOPHARYNGEOM 2007. Standardization of surgical reports including specific assessment of tumor/damage location is recommended.

The authors have no relevant relationships to report.

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Nonfunctional Pituitary Adenoma Diagnosed During Pregnancy with Progressive Visual Impairment: A Clinical Case

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Nonfunctional pituitary adenomas (NPA) have an incidence of 0.59 cases/100.000 pregnancies in the UK. It can be previously known or newly diagnosed with symptoms of enlargement; only few cases have been described with visual impairment, treated with either cabergoline or surgery. We present a case of NPA diagnosed during pregnancy with chiasmatic compression that required surgery. **Clinical case**: A 37-yr-old woman was evaluated with history of 3 months of visual disturbance. On examination, visual acuity was reduced on right associated to an afferent pupil defect and paracentral scotomas on campimetry. Patient refused MRI because she suspected pregnancy. She came back two months later coursing 13th week pregnancy with progression of visual field defects and a new campimetry showed enlargement of paracentral scotomas on the right eye. Non-enhanced MRI showed a 19 x 21 mm pituitary mass compressing the left optic nerve and chiasm. Patient denied headache, previous oligomenorrhoea or galactorrea. Hormonal evaluation showed: prolactin 37.2ng/ml (NV <25), TSH 3.6uU/ml, fT4 0.89ng/dl (NV 0.93-1.7), IGF-1 91.7ng/ml (NV 57-241), cortisol 11.8µg/dl and 25.7µg/dl post ACTH stimulation test. Since visual symptoms were present two months before pregnancy and visual field defects were confirmed at the beginning of pregnancy, we assumed cabergoline treatment could not solve the compression of optic nerve and chiasm. Transphenoidal resection was performed without any complication. Biopsy showed null cells adenoma with ki67 4%. One month after surgery, campimetry was normal. A healthy child was delivered at 39 weeks of gestation. Two months after delivery, MRI showed no residual tumor, campimetry persist normal and the patient had normal pituitary function and normal breast-feeding. **Conclusion**: Management of NPA with visual field defect during pregnancy is a challenge. Our case presented with unusual early visual field defects and this could be a reason to prefer surgery instead of cabergoline.

The authors have no relevant relationships to report.

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Outcome of Prospective Observation Alone in 128 Patients with Presumed Clinically Nonfunctioning Pituitary Adenoma

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In patients presenting with a sellar mass consistent with an adenoma on imaging without clinical or biochemical evidence of hormone excess, a clinically nonfunctioning pituitary adenoma (CNFPA) is the most likely diagnosis. Many patients with a CNFPA lack signs or symptoms of mass effect necessitating surgery, but the outcome of observation alone for such patients has rarely been studied. We conducted a prospective, observational study of patients who elected, along with their physician, to follow their tumor without surgery. Inclusion criteria included tumor size ≥ 6mm and normal prolactin for tumors <10 mm and prolactin < 100 ng/ml for those ≥ 10mm. History, exam, labs and imaging were characterized at baseline and longitudinally. Intervals for follow up pituitary MRIs were suggested, but these were done as prescribed by each patient's physician. Data are given as median(range). We enrolled 128 patients aged 56.5 yr. (24-84) and 58% female. At presentation, 70% had CNFPAs ≥ 10mm (15.6;10-40) and 30% were <10 mm (7; 6-9). On follow up MRI at 2.57 yr. (0-8.3), 43.6% of tumors grew, 7% decreased in size and 49.4% were unchanged. Of tumors that enlarged, the rate of increase was 0.85 mm/yr. (0.12-7.4). A subset of 25 patients underwent pituitary surgery after 2.43 yr. (0.4 -7.6) of follow up. In this subset, tumor growth was 1.1 mm/yr. (0.16-7.4). Reasons for surgery were tumor growth to abut or compress the optic chiasm (n=18), increased suprasellar extension (n=7) and apoplexy (n=1). In summary, in this prospective study of patients with apparent CNFPA followed with an observation-only treatment approach, the rate of tumor growth was slow in most patients (≤ 1.5mm/yr. in 86% of patients), but 19.7% did proceed with pituitary surgery. Additional longitudinal follow up is needed to fully determine the outcome of CNFPAs treated initially with observation alone.

The authors have no relevant relationships to report.

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Pituitary Adenoma and Turner Syndrome: Association or Coincidence?

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Background: Turner syndrome (TS) affects 1/2,500 women. Clinically significant pituitary adenomas (PA) are observed in approximately 1/1000 people; precise prevalence is unknown. **Methods:** We describe 2 cases (female) with TS and PA followed in clinic, and a literature review. **Results:** Case 1: 33yo presented with intermittently elevated LH/FSH (151.5/75.8mIU/mL); a microPA (3.7x6.8 mm) was found after oligomenorrhea, hot flashes, weight loss, and visual disturbance complaints. Except for hypergonadotropic hypogonadism, pituitary axes were normal. MRI 2 years later showed stability. Karyotype revealed mosaic TS and estrogen/progesterone replacement therapy was started. Case 2: 39yo diagnosed with TS and primary hypothyroidism at age 14 years, treated with GH until 22 years and oral birth control briefly at 15 years. MRI for headaches revealed 21x22x19mm PA with subacute hemorrhage and optic chiasm compression. Prolactin was minimally elevated, GH and cortisol axes normal, including 24hr UFC. Post transsphenoidal surgery (TSS), pathology confirmed PA. Residual tumor grew significantly over 14 months; IGF-1 was low, prolactin, cortisol and ACTH were normal. Pathology after 2nd TSS showed recurrent corticotroph PA; further evaluation for hypercortisolism is pending. Literature review revealed 11 cases of PA in TS: 3 GH-, 2 prolactin-, 1 ACTH-secreting, 3 non-functioning, 2 with unknown hormone status (one GH/PRL on pathology). Additionally, 3 post-mortem silent corticotroph microadenomas and 1 corticotroph hyperplasia were reported. **Discussion:** Though gonadotroph hyperplasia would be expected in TS, similar to thyrotroph and corticotroph in untreated hypothyroidism and Addison's disease, only few cases of PA or hyperplasia are reported in TS, none of which were gonadotroph. From these cases and literature review, frequency of corticotroph and somatotroph adenomas seems to be higher than expected, however, causality or association is unknown. **Conclusion:** To date, there is no proven pathological link between TS and PA. Work-up for PA in patients with TS should be performed based on clinical suspicion of pituitary dysfunction.

The authors have no relevant relationships to report.

P47
Pituitary Apoplexy as First Presentation of IgG4 Related Disease

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Introduction: Pituitary gland involvement in IgG4-related disease (RD) has been described and commonly misdiagnosed as a non-functional pituitary adenoma. We present a patient with pituitary apoplexy as the first presentation of IgG4-RD. **Case report:** A 49 year old woman with type 2 DM presented to emergency department with abdominal pain, nausea, vomiting, and significant weight loss over 1 month. Her vital signs were stable, she appeared euvolemic with an unremarkable physical examination. A biochemistry panel revealed hyponatremia 118 mmol/L (normal 135-145mmol/L). Further investigation for causes of hyponatremia disclosed low am cortisol of 20 (N:100-500 nmol/L) & low ACTH < 0.2 (N:1.6-13.9 pmol/L), TSH was 0.04 (N:0.4-4 mIU/L), Free T4 9.5 pmol/L (N:9-26), FSH 2.5 U/L (N: 48.6-143.9), E2 < 18 pmol/L (N: 0-145). The profile was consistent with combined pituitary hormone deficiencies. An MRI revealed a pituitary macroadenoma measuring 13.5 x 9 x 11 mm with hemorrhagic transformation/apoplexy. She was stabilized and placed on hormone replacement therapy (hydrocortisone and levothyroxine) before undergoing trans-sphenoidal surgical resection of pituitary tumor. The pathology revealed IgG-4-related hypophysitis with no evidence of an adenoma. **Discussion:** IgG4-RD is a fibro-inflammatory condition characterized by a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and, often but not always, elevated serum IgG4 concentrations. Commonly it's confined to a single organ but multiorgan involvement also occurs. Pituitary involvement in IgG4-RD has been described as pituitary hypophysitis. MRI findings commonly reveal both pituitary gland and stalk enlargements. Apoplexy has been recently reported in the literature as an atypical, uncommon presentation of IGG4- related hypophysitis. **Conclusion:** Pituitary apoplexy, panhypopituitarism in the context of a non-functioning pituitary adenoma should be considered as rare and unusual presentations of IGG4-RD.

The authors have no relevant relationships to report.

P48
Predictors of Pituitary Tumour Recurrence and Aggressiveness

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Classification of pituitary tumours is a dynamically evolving area. **Objectives:** To determine the clinical utility of predictive factors in pituitary tumour prognostication. **Methods:** Retrospective evaluation of patients from Oxford University and St Vincent's Hospitals, between 1989 and 2017. Adult patients with histopathology and at least 6 months clinical data were included. Pituitary tumour Tissue Micro-Arrays (TMAs) were created. Proliferative markers and transcription factors were assessed by immunohistochemistry (IHC). Patient clinical and radiological records were reviewed. Between group differences were assessed by Chi-square and Mann-Whitney U tests. Cox and binary regression were used to identify predictors of behaviour. **Outcomes:** (1) tumour recurrence (radiological or re-intervention twelve months post-operatively) and (2) "aggressive behaviour" (four interventions, Nelson's Syndrome or carcinoma). **Results:** 449 patients met inclusion criteria, median age was 55 years, 54% were male and median follow up was 93 months (range 7-1344). 414 (92%) were first operations, 287 (64%) were clinically non-functioning, 217 (52%) demonstrated invasiveness (sphenoid and/or cavernous sinus) and 33 (7%) required four interventions. Transcription factors were evaluated in 207 tumour samples total, of which PIT-1, ER and T-PIT were assessed in 67, 81 and 80 of above patients respectively. There were seven null cell tumours on hormonal IHC, of which one expressed PIT-1, four ER and one T-PIT. Recurrence was predicted by invasiveness (HR 1.6, P=0.025) and elevated mitotic count (HR 2.5, P=0.003). Aggressiveness was predicted by elevated Ki67 (Ki67 3-10% (OR 2.6, P=0.025), Ki6710% (OR 8.8, P=0.006)), mitotic count (OR 3.4, P=0.015) and Trouillas Grade (2b) (OR 5.3, P=0.009). **Conclusions:** Identified predictors of recurrence include invasiveness and elevated mitotic count. Predictors of aggressiveness include elevated Ki67, mitotic count and Trouillas Grade (2b). Evolving classification of Pituitary tumours will lead to improved prognostication and more personalised post-operative management.

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P49
Suprasellar Cavernous Hemangioma: Case Report

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Introduction: Cavernous hemangiomas are vascular malformations that occur in approximately 0.5 to 1.0% of the population. They are most commonly encountered in the supratentorial region (80%), however in the suprasellar region they are rare, accounting for only 4% of cases. **Case Report:** A 25-year-old male patient presented sudden headache, blurred vision and epistaxis followed by nasal dripping and dizziness for three days. Worsening of headache and an onset of disorientation led him to seek medical assistance. A brain magnetic resonance imaging showed an expansive hypothalamic-chiasmatic lesion, heterogeneous, with bleeding in different stages of evolution, marked T2* hypointensity (residual hemorrhage), peripheral T2 hypointensity, measuring 2.2 x 2.9 x 2.6 cm. The pituitary gland and optic chiasm were normal. The pituitary stalk was not visualized. Rare calcification foci were seen on computed tomography. The patient had a normal confrontation visual field, 8 am serum cortisol of 10.30 mcg/dL, insulin-like growth factor I of 156 ng/mL [normal range (NR): 83-259], prolactin 38.67 ng/mL (NR: 2.60-13.10), free T4 0.78 ng/dL (NR: 0.54-1.24) and total testosterone 266 ng/dL (NR: 75-781). A transcranial surgery was performed with subtotal removal of a bleeding cavernoma-like material with calcified areas. Histopathological examination revealed a dark-red material with juxtaposed vessels of different calibers, along with gliosis with scattered hemosiderin-laden macrophages in the surrounding cerebral tissue. In the post-operative setting, he presented diabetes insipidus, hypogonadism and hypothyroidism. **Discussion:** Our patient was diagnosed with a suprasellar cavernous hemangioma (SCH) which is not a common location as few cases have been reported to date. Differential diagnosis must include craniopharyngiomas. However, a "popcorn-like appearance" characterized by heterogenous intensities on T2-weighted images surrounded by a hypointense rim is suggestive of SCH. Thus, a preoperative diagnosis of cavernomas is challenging. A correct diagnosis is crucial for proper post-operative management.

The authors have no relevant relationships to report.

P50
Two Cases of Pituitary Abscess in a Rathke´s Cleft Cyst

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Pituitary abscesses are a rare life-threating disease that can be seen in previously healthy pituitary or affected by tumoral lesions such as Rathke's Cleft Cysts (RCC). **Case 1:** A 51 year-old woman with a completely resected RCC 12 years earlier and normal pituitary function. After acute sinusitis, she presented unmanageable nonfebrile headache and a III nerve palsy. MRI revealed 2 cystic lesions of 13 and 22mm with a contrast-enhanced rim without visual impairment. Hypopituitarism without diabetes insipidus and slightly altered C-reactive protein (CRP) were evidenced. She underwent endoscopic transsphenoidal surgery (TSS) where a defect in sellar floor and pus were observed. Cultures confirmed a *Staphylococcus aureus* infection. She received Cloxacillin for 3 weeks and developed transient diabetes insipidus. After 3 months, MRI revealed no lesions and normal pituitary function. **Case 2:** Previously healthy 19 year-old woman referred due to 1 month nonfebrile headache and galactorrhea. MRI revealed an 18mm cystic lesion, with an intraluminal T1-hyper and T2-hypointense nodule and a contrast-enhanced rim without visual impairment. Normal CRP, mild hyperprolactinemia and hypopituitarism without diabetes insipidus were detected. TSS was performed, showing pus and colloid-like material. Cultures confirmed *Staphylococcus aureus* and *epidermidis* infection and biopsy confirmed an infected RCC. She received Cloxacillin for 3 weeks. After 3 months, MRI revealed no lesions, she had regular menses and normal serum cortisol with persistent central hypothyroidism and asymptomatic mild hyperprolactinemia. **Conclusion:** Pituitary abscesses are rare pituitary lesions that can develop in normal or previously altered pituitary gland. Typically, it presents with headache, hypopituitarism, diabetes insipidus and a cystic lesion in the MRI, but usually without fever or systemic inflammation, so it is crucial to have a high level of suspicion. Usually it requires hormonal management and TSS with parenteral antibiotics. Although in most cases hypopituitarism persists, both our patients had a successful evolution.

The authors have no relevant relationships to report.

P51
Significant Peri-tumoral Inflammation in Craniopharyngiomas Mimicking Hypophysitis: Two Case Reports

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Objective: Craniopharyngiomas are tumors of sellar region arising from remnants of Rathke's pouch; adamantinomatous craniopharyngioma (AC) mostly affecting pediatrics, and papillary craniopharyngioma (PC) affecting adults. Lymphocytic hypophysitis (LH) typically involves an autoimmune predisposition and glucocorticoids (GC) may decrease tumor size and/or symptoms. However, severe headaches and hypopituitarism are frequent in both. Here, we report 2 patients with infundibular lesions diagnosed, based on initial pathology with LH; PC was subsequently confirmed. **Cases/Results:** Case 1: A 51-year-old female presented with severe headaches (6 months) and new visual field (VF) defects. Brain MRI showed 5mm cystic infundibular thickening extending to the hypothalamus. Simultaneously, she was prescribed prednisone 15mg daily for polymyalgia rheumatica; prednisone induced rapid headache and VF improvement. However, the stalk lesion increased in size (over 4 months) and patient underwent transsphenoidal surgery (TSS); pathology revealed LH and no tumor. Headaches recurred and prednisone was increased (mean dose 20-40mg for 6 months), which initially achieved tumor stabilization and headache control. Subsequently, brain MRI showed further progression with optic chiasm compression and patient underwent a craniotomy. Pathology report confirmed PC. Headaches improved immediately post-operatively and patient continues on adrenal and thyroid replacement. Case 2: A 71-year-old male with a 1cm stalk nodularity, presented with headaches and panhypopituitarism with diabetes insipidus. A stalk lesion biopsy revealed polyclonal lymphocytic infiltration with macrophages; patient refused high-dose GC. Over 3years, the lesion progressively doubled and headaches recurred. Pathology post-TSS showed PC with abundant xanthogranulomatous changes and patient continues to be panhypopit. **Conclusions:** Management of stalk lesions is challenging. Differential diagnosis includes LH, but craniopharyngiomas can also prompt peri-tumoral inflammation. Xanthogranulomatous changes may be associated with cholesterol clefts, mostly with AC. Headaches and/or hypopituitarism could be due to lymphocytic infiltration. Increased awareness regarding craniopharyngiomas hypophysitis-like signs and symptoms in some patients is needed to guide treatment (surgery vs high- dose GC).

The authors have no relevant relationships to report.

PITUITARY FUNCTION

P52
A Rare Case of a Functional Gonadotroph Pituitary Adenoma

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Introduction: Pituitary adenomas can be classified as clinically functioning or non-functioning. About 64% of non-functioning pituitary adenomas are found to be gonadotroph adenomas. We present a case of a functional gonadotroph pituitary adenoma causing symptoms from gonadotroph hypersecretion. **Case:** A 43-year old woman was incidentally found to have a 7 x 6 mm pituitary lesion in 2011. Repeat MRI in 2013 showed the adenoma size was stable. In 2016, she reported worsening headaches, fatigue, 20 lbs weight gain and irregular menses. She later became amenorrheic. She was seen at our endocrinology clinic in 2017. MRI pituitary showed increase in size of her pituitary adenoma to 14 x 12 mm, which was now abutting the optic chiasm. She had occasional blurry vision; formal visual field exam revealed a small defect. Hormonal work up revealed FSH 36 mIU/mL, LH 8.9 mIU/mL and estradiol 48.2 pg/mL. Her other pituitary axes were intact. Due to her young age and potential for worsening vision, she underwent trans-sphenoidal resection of the adenoma in 2018. Her post-op course was uneventful. Pathology revealed positive staining for hCGa, LH and FSH; the Ki-67 index was 2%. On her 6-month post-operative visit, she reported having regular menses, her FSH had come down to 23.4 mIU/mL and her estradiol was higher 82.7 pg/mL. **Discussion:** Pituitary gonadotroph adenomas are mostly non-functioning clinically, but in rare cases can cause symptoms of hormonal hypersecretion. This case highlights the importance of pre- and post-operative endocrine work up in patients with pituitary adenomas.

The authors have no relevant relationships to disclose.

P53

Different Mode of Anterior Pituitary Function Deterioration Including Adrenal Axis Insufficiency in the Families/Sporadic Patients with PROP1 Mutation, Over 30 Years of Single Center Longitudinal Observation

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The PROP1 gene mutation is the most frequent genetic defect in patients with multiple pituitary hormone deficiency. However, the time, degree and mode of pituitary function deterioration is not fully known and understood. **Aim:** To investigate the time and mode of pituitary function deterioration in the families/sporadic patients with PROP1 mutation during longitudinal observation. **Methods:** We performed a retrospective longitudinal (33 years(SD=12) analysis of 22 patients (11M/11W with PROP1 mutation, including 5 families (13/22, 59 % of investigated population), with 2-3 affected siblings who were under medical supervision of the pediatric/adult endocrinology departments of our university. **Results:** All patients initially presented with growth failure at mean age (MA) 7.4 years (SD=4,3). 14/22 patients were first diagnosed with GH/ TSH deficiency simultaneously and replacement therapy was instituted MA 6.6years (SD=3.0). 5/22 (older patients) received delayed/intermittently GH treatment. Gonadal deficiency was diagnosed in 22/22 patients MA 15.6 years (SD=5.1). 17/22 (77%) patients developed adrenal deficiency MA 23.9 years (SD=16.6). The age of deficiencies determination in siblings are given in the table.

Families	Sex/ Actual age	Age when insufficiency was diagnosed			
		HGH	**TSH**	**LH/FSH**	**ACTH**
1	F/25	5	5	16	7
	M/19	4	1	12	12
2	M/35	9	8	16	16
	M/33	5	5	15	No
	M/29	4	2	14	No
3	M/52	5	5	5	46
	F/42	3	3	19	29
	F/40	5	16	16	31
4	F/39	8	8	15	No
	M/37	6	6	27	No
5	F/24	4,5	5	15	No
	F/22	4,5	4,5	16	16
	M/20	4,5	4	14	10

Conclusions: The pituitary function deteriorates progressively in patients with PROP1 mutation, however there is no specific order of deterioration even among affected siblings. The adrenal axis can deteriorate long after other axis insufficiencies, however there are patients with no adrenal insufficiency even during lifelong observation. Patients with PROP1 mutation should be carefully monitored for possible adrenal insufficiency regardless of the time of observation.

The authors have no relevant relationships to report.

P54

Evaluating Early Moderate Fluid Restriction and the Risk of Delayed Hyponatremia Following Pituitary Surgery

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Background/Objective: A potentially serious complication of transsphenoidal surgery (TSS) is delayed hyponatremia, defined as hyponatremia occurring 3 to 14 days after surgery. Delayed hyponatremia occurs in up to 35% of patients, and if severe, can be life-threatening and lead to hospital readmission. We conducted a prospective pilot study comparing two approaches of postoperative fluid management and hypothesized that patients treated with early moderate postoperative fluid restriction would have decreased rates of delayed hyponatremia. **Methods**: Patients scheduled for TSS were randomly assigned to a control group (CON, n=40) or experimental group (EXP, n=49). Patients with diabetes insipidus were excluded. All patients were started on postoperative weight-based intravenous fluid until POD 1 and allowed to drink water freely. Patients in the EXP group were fluid restricted to 1.8 liters/day (2 liters/day if weight > 100kg) starting POD 3 until POD 14, and control patients were instructed to drink *ad lib*. Serum sodium (Na) levels were checked every 8 hours in the hospital and on POD 7, 10, and 14. Lowest Na between POD 3 and POD 14 was determined and incidence of mild (130-134 mEq/L), moderate (125-129 mEq/L) and severe (< 125 mEq/L) hyponatremia was evaluated. Mann-Whitney U, chi-square and Spearman's rho tests were used for statistical analyses. **Results**: Although lowest median Na was similar between groups (EXP 138 mEq/L vs CON 137 mEq/L, p=0.398), there was a trend toward an overall decreased incidence of delayed hyponatremia in the EXP (25%) group compared to the CON (31%) group (p=0.558). No correlation was found between postoperative day and hyponatremia. **Conclusion:** Preliminary results from this study suggest that patients treated with early moderate postoperative fluid restriction after TSS may be less likely to develop delayed hyponatremia. Future studies with more patients, and perhaps more aggressive fluid restriction, are needed to further determine clinical significance.

The authors have no relevant relationships to report.

P55

Low Plasma Oxytocin Levels and Increased Psychopathology in Hypopituitary Men with Diabetes Insipidus

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Background: Oxytocin (OT), a hypothalamic-posterior pituitary hormone with important neuropsychiatric properties, shares anatomical pathways of synthesis and secretion with vasopressin. While patients with central diabetes insipidus (CDI) are presumably at risk for OT deficiency, an OT-deficient state in patients with hypopituitarism has not been established. We hypothesized that in men with CDI compared to (1) patients with similar anterior pituitary deficiencies but no CDI (APD) and (2) healthy controls (HC) of similar age and BMI, plasma OT levels would be lower and psychopathology would be higher. **Subjects and Methods:** This was an institutional review board-approved cross-sectional study in a clinical research center. Sixty-two males (20 CDI, 20 APD and 22 HC) age 18-60 years were enrolled. Fasting frequent sampling of blood was performed every 5 min over 1-hour for OT and validated questionnaires were administered to assess for psychological symptoms and quality of life. One-way analyses of variance followed by Fisher's least significant difference for pairwise comparisons and Spearman rank correlation test were performed. R**esults**: Mean 1-hour pool of fasting OT levels were lower in CDI compared to APD and HC (p=0.02 and p=0.009, respectively) with no differences between APD and HC (p=0.78). Symptoms of depression, anxiety and alexithymia were more pronounced in CDI (p=0.001; p=0.004; p=0.02, respectively) than HC. While CDI and APD reported worse physical health compared to HC (p=0.001 and p=0.005) with no differences between APD and CDI, only CDI reported worse mental health compared to HC (p=0.004). **Conclusions**: We demonstrate low plasma OT levels and increased psychopathology in hypopituitary men with CDI, suggestive of a possible OT-deficient state. Larger studies in both genders are required to confirm these findings and clinically characterize patients with hypopituitarism and OT deficiency.

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P56
Periostin Concentrations in Childhood-onset Craniopharyngioma Patients

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Purpose*:* Periostin is highly expressed in craniopharyngioma (CP)-associated fibroblasts and has been identified as a marker for Non-Alcoholic Fatty Liver Disease (NAFLD). Half of CP patients with hypothalamic syndrome develop NAFLD. We hypothesized that periostin concentration is elevated in biological fluids of CP and associated with pathological hepatic parameters, indicating increased risk for NAFLD. **Methods:** Cross-sectional study on 35 patients with sellar masses (SMP) recruited in the German Childhood Craniopharyngioma Registry (32 CP, 2 xanthogranuloma, one pilocytic astrocytoma), 3 short-statured patients with isolated growth hormone deficiency, 5 short-statured patients with normal findings in GH-stimulating tests and decreased insulin-like growth factor (IGF)-1 and 7 healthy controls. Periostin was measured by Elisa in serum, urine and saliva. **Results:** Periostin serum, urine and saliva concentrations in CP were similar to concentrations of the other groups. Hypothalamic involvement/hypothalamic lesions, degree of obesity as well as hepatic enzymes were not associated with elevated periostin concentrations. Due to low patient numbers with pathological hepatic parameters, missing imaging data on the degree of steatosis hepatis and the lack of histological proof of NAFLD no definitive conclusions can be drawn from measured periostin concentrations in serum. Interestingly, the subgroup of patients with decreased IGF-1 levels showed elevated concentrations of serum periostin when compared with other groups. **Conclusions:** In CP, periostin concentrations are not associated with known risk factors for NAFLD such as hepatic and metabolic parameters, obesity and hypothalamic lesions. Accordingly, periostin does not seem to be a suitable marker for NAFLD in CP.

The authors have no relevant relationships to report.

P57
Regression of Radiological Changes in a Patient with Newly Diagnosed Diabetes Insipidus and Deficiency of Somatotropin and Gonadal Axis - Clinical Case

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Hypophysitis is an inflammation involving pituitary gland and the stalk. The disease may be primary or secondary, most often occurs with symptoms resulting from pituitary enlargement, hormonal disturbances and diabetes insipidus. Hypophysitis characterizes with typical radiological changes. Due to the rarity of the disease (~1 in 9 million cases/probably underestimated) there are no clear guidelines. In therapy, besides hormonal substitution, an awaiting approach, high-dose steroid or other immunosuppressant drug therapy are used as well as surgery or radiotherapy in rare cases. We present a case of 22-year old patient, without chronic diseases, who developed significant polyuria and polidypsia in December 2017. He associated the symptoms with respiratory tract infection. Patient denied head trauma. Diabetes insipidus was diagnosed in April 2018, with improvement after desmopressin administration. In pituitary MRI the thickening of the stalk (4,5 mm) and lack of posterior pituitary lobe signal were described. During several hospitalization in Endocrinology Department we confirmed adequate control of diabetes insipidus, well-functioning adrenal and thyroid axes, gonadal and somatotropin axes deficiencies and mild hyperprolactinemia. In the chest CT no abnormalities were found, the tuberculosis was also excluded. In VI 2018 in MR the stalk was enlarged to 5x5x5 mm, with normal image of pituitary lobes. The lymphocytic hypophysitis was diagnosed. Due to the small severity of symptoms the decision about further observation was made. Subsequently, patient was hospitalized twice (IX 2018 and I 2019) – the reduction of stalk size (3x3x3,8 mm) in control MR with normalization of IGF-1, prolactin and testosterone values and persistent diabetes insipidus were observed. Radiological and hormonal improvement seems to confirm that an awaiting approach could be a treatment option in patients with hypophysitis. Further research is needed to create algorithms for the management of pituitary inflammation.

The authors have no relevant relationships to report.

P58
Retrospective Study on Silent Corticotroph Adenomas: A Diverse Gamut of Disease

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Objective: Silent corticotroph adenomas (SCAs) behave more aggressively than other non-functioning adenomas (NFAs). This study aims to expand the body of knowledge of the behavior of SCAs. **Methods:** A total of 196 non-corticotroph NFAs and 20 SCAs were included in this IRB approved retrospective study of all resected pituitary adenomas from 2012-2017. Adenomas were grouped by immunohistochemical staining. Demographics, clinical presentation, imaging and biochemical data were gathered. The primary endpoint was to compare features of SCAs vs. other NFAs that suggest aggressive disease, including pre-surgical comorbidities, postoperative complications, extent of tumor and recurrence. Statistical analysis was performed using SAS, T-test, Chi-Square and Fisher's Exact Tests were employed where applicable in univariate analyses. Logistic regression was used to determine significant predictors using all variables in corresponding univariate analysis with a significance level of $p<0.1$. Covariates were maintained in the model if a contributing significance level of $p<0.05$ was achieved. Variables with less than 25% missing data were included in regression analysis. **Results:** With multivariate regression analysis, SCAs showed higher rates of hemorrhage on preoperative imaging than NFAs ($p=0.017$). In univariate analysis, SCAs presented with headache, vision changes and fatigue ($p=0.012$, $p=0.041$, $p=0.028$). On MRI, SCAs exhibited greater extent of tumor burden with increased occurrence of stalk deviation, suprasellar invasion, optic chiasm compression and cavernous sinus invasion ($p=0.008$, $p=0.021$, $p=0.022$, $p=0.015$). 30% of SCAs were noted to recur with a 14% recurrence rate in other NFAs, though this difference was not of statistical significance ($p=0.220$). The significance of the univariate data was limited by the power of this study. **Conclusions:** SCAs exhibit features of more aggressive disease, including increased rates of hemorrhagic lesions, preoperative symptoms and greater tumor burden. Interestingly, a significant increase in recurrence was not seen despite these features.

The authors have no relevant relationships to report.

P59
The Role of Dynamic Imaging Techniques in Preoperative Diagnosis of Silent Corticotroph Adenomas

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Objectives: Silent corticotroph adenomas (SCAs) present as non-functioning adenomas (NFAs) with no clinical evidence of hypercortisolemia but are immunopositive for adrenocorticotrophic hormone (ACTH) on pathology. Pooled results from a recent review by Melmed et al demonstrated 25-40% of SCAs present with cavernous sinus invasion, preoperative hypopituitarism, and tumor recurrence. Imaging features of SCAs include macroadenomas with multiple microcysts on T2-weighted MRI (although microcysts are also seen in NFAs), cavernous sinus invasion and frequent intratumoral hemorrhage compared to NFAs. Golden-angle radial sparse parallel (GRASP) technique acquires all dynamic information in a single, continuous scan with high spatial and temporal resolution. Surgery is first-line treatment; SCAs are aggressive, locally invasive tumors that often recur and might warrant extensive surgical resection, including resection of intracavernous component. GRASP may be helpful in the preoperative evaluation of SCAs. **Our aim is** to evaluate the role of Permeability - GRASP imaging in the management of SCAs. **Methods:** Retrospective single-center IRB-approved study of (n=216) NFAs over the last 5 years. Of these, 20 were SCAs and 196 were other NFAs. All studies were obtained on Siemens 3T scanners (Skyra and VIDA) using a dynamic MR protocol. GRASP imaging was obtained to evaluate for permeability by AUC (area under the curve) and Peak measures in a sample of SCAs (n=5) and other NFAs (n=11). Statistical analysis was performed using SAS, Student's T-test, Chi-Square and Fisher's Exact tests were employed for univariate analyses. **Results:** On GRASP imaging, SCAs showed significantly lower permeability measures by both AUC (Mean AUC SCA: 0.106, NFA: 0.0713, $p=0.001$) and Peak (Mean Peak SCA: 0.110, NFA: 0.733, $p<0.001$) measurements. This is likely secondary to the predominantly cystic appearance of SCAs relative to NFAs ($p=0.029$). Additionally, SCAs were associated with significantly reduced contrast enhancement ($p=0.002$). **Conclusion:** GRASP imaging utilizing permeability AUC and Peak measures successfully distinguishes SCAs from other NFAs.

The authors have no relevant relationships to report.

P60

Association Between Prolactin Level and Tumor Size Reduction at 3 Months After Cabergoline Treatment in Patients with Macroprolactinoma

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Objectives: Prolactin (PRL) normalization after 3 months of Cabergoline (CAB) treatment are useful predictors of responsiveness in patients with prolactinoma. However, differences within the PRL normalization cut-off value have not been identified. **Methods:** We reviewed the medical records of patients with prolactinomas who were treated with CAB as a primary drug at Severance Hospital. We included patients who had a full dataset of pituitary hormone assays and sella MRI at baseline, follow-up PRL assay and sella MRI at 3 months after CAB treatment. **Results:** Among the 217 patients, 123 patients had macroprolactinoma. After 3 months of CAB treatment, PRL normalization was achieved in 109 (88.6%) of macroprolactinoma patients, the mean size reduction was 22.9%. We divided these patients into two groups according to the PRL level at 3 months. When we classified by 5ng/mL, low normal group (PRL≤5, n=82) and high normal group (5<PRL≤20, n=27) did not differ in baseline PRL, tumor size and size reduction. When we classified by 1ng/mL, low normal group (PRL≤1, n=49) and high normal group (1<PRL≤20, n=60) did not differ in baseline PRL and tumor size. However, size reduction was significantly different between the two groups (27.18±18.31 vs. 19.46±13.87%, P=0.014). Even if we narrow down the high normal group (1<PRL≤10, n=50 and 1<PRL≤5, n=33), similar results came back (27.18±18.31 vs. 19.30±13.66%, P=0.017 and 27.18±18.31 vs. 19.22±14.33%, P=0.039). **Conclusion:** Prolactin drops to less than 1ng/ml at 3 months after CAB treatment predicts better response of macroprolactinoma.

The authors have no relevant relationships to report.

P61

Change of T2-weighted Intensity of Prolactinoma as a Predictable Value for Relapse of Hyperprolactinemia After Cabergoline Withdrawal

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Background: The aim of this study was to assess whether change of T2 weighted signal intensity (T2-WSI) on magnetic resonance imaging (MRI) is associated with complete remission after cabergoline withdrawal in patients with prolactinoma. **Methods:** We identified 631 patients with hyperprolactinemia and pituitary adenoma from 2005 to 2018. Of 631 patients, 35 patients who stopped the cabergoline medication were included in final analysis. We measured T2-WSI of both adenoma and normal portion of pituitary gland on the initial and 6-month follow up MRI using the Picture Archive Communication System. The patients were divided into 2 groups, based on the maintenance of normal prolactin level or relapse after withdrawal of cabergoline. **Results:** Only 20% patients relapsed at 6(3-63) months after drug withdrawal in the 14(5-97) month follow-up period. In order to see whether the change of T2-WSI between initiation of treatment and six-month follow up was different between recurrence group and remission group, we performed a one by two (signal intensity of both MRI) repeated measures analysis of variance using recurrence as a between-subject factors. Result showed that there were no significant main effect of treatment (F (1,33)=2.491, p=0.124). However, there was a significant difference of T2-WSI by treatment interaction, which means that a treatment effect was different between recur and non-recur groups (F(1,33)=4.783, p=0.036). T2-WSI in remission group was significantly decreased after 6 months of treatment (Z=2.03, singned rank=292, p=0.043), but not in recurrence group (signed rank=9, p=0.469). **Conclusions:** In this study, the change of T2WSI was associated with relapse of hyperprolactinemia in patients with prolactinoma after withdrawal of cabergoline.

The authors have no relevant relationships to report.

P62
Giant Prolactinomas: Characteristics in Presentation and Evolution

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Introduction: Among prolactinomas, 16% are characterized as giants, defined as those with ≥4cm on the largest axis, in association with a Prolactin (PRL) value greater than 1000 ng/mL. **Objective**: To report the presentation/evolution of individuals with giant prolactinoma. **Patients and Methods**: This retrospective study was performed at a university-affiliated Center of Neuroendocrinology of southern Brazil. Between 2001 and 2018, eleven patients with giant prolactinoma were identified. **Results**: The study population consisted of 6 males and 5 females with age between 18 and 68 years. The pituitary lesion was an incidental finding in 2 cases. The most prevalent manifestations were visual complaints (7 cases), headache (6) and obesity (7/10 cases). The main hormonal deficits were gonadal (10) and thyroid (6). The largest axis of the adenoma ranged from 4 to 8.5 cm and the PRL level from 1500 to 17,716 ng/mL. In 9 cases the tumor was invasive. Hemianopsia or extinct field were observed in 9 cases. All the patients used bromocriptine (3 cases) or cabergoline (8), 4 patients underwent surgery and one patient underwent radiotherapy. Follow-up ranged from 7 months to 17 years. In the last evaluation, the PRL was normal in 5 cases and elevated in the others (3 of them in values lower than 100ng/mL). In the last image (8 patients), there was empty sela in one case, absence of lesion in one and a noninvasive lesion in 3. **Conclusions**: In this sample of patients with giant prolactinomas, contrary to that reported in the literature, we observed equivalence between the number of men and women, and high prevalence of central hypogonadism, hypothyroidism and obesity. On the other hand, despite excess tumor size and hormonal hypersecretion, the disease progressed with normal or minimally elevated PRL values in 72% of cases and regression of invasive characteristics in 67%.

The authors have no relevant relationships to report.

P63
Results of Biopsy-proven Sellar Germ Cell Tumors: 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 sellar germ cell tumors. 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 sellar germ cell tumors (GCTs). **Methods:** From January 2008 to December 2015, 61 patients who were histologically diagnosed as sellar GCTs 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 sellar GCTs 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 sellar GCTs, while the combination of chemotherapy and RT was associated with a better prognosis.

The authors have no relevant relationships to report.

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Pituitary Master Course Essentials of Pituitary Diseases for Fellows-in-Training

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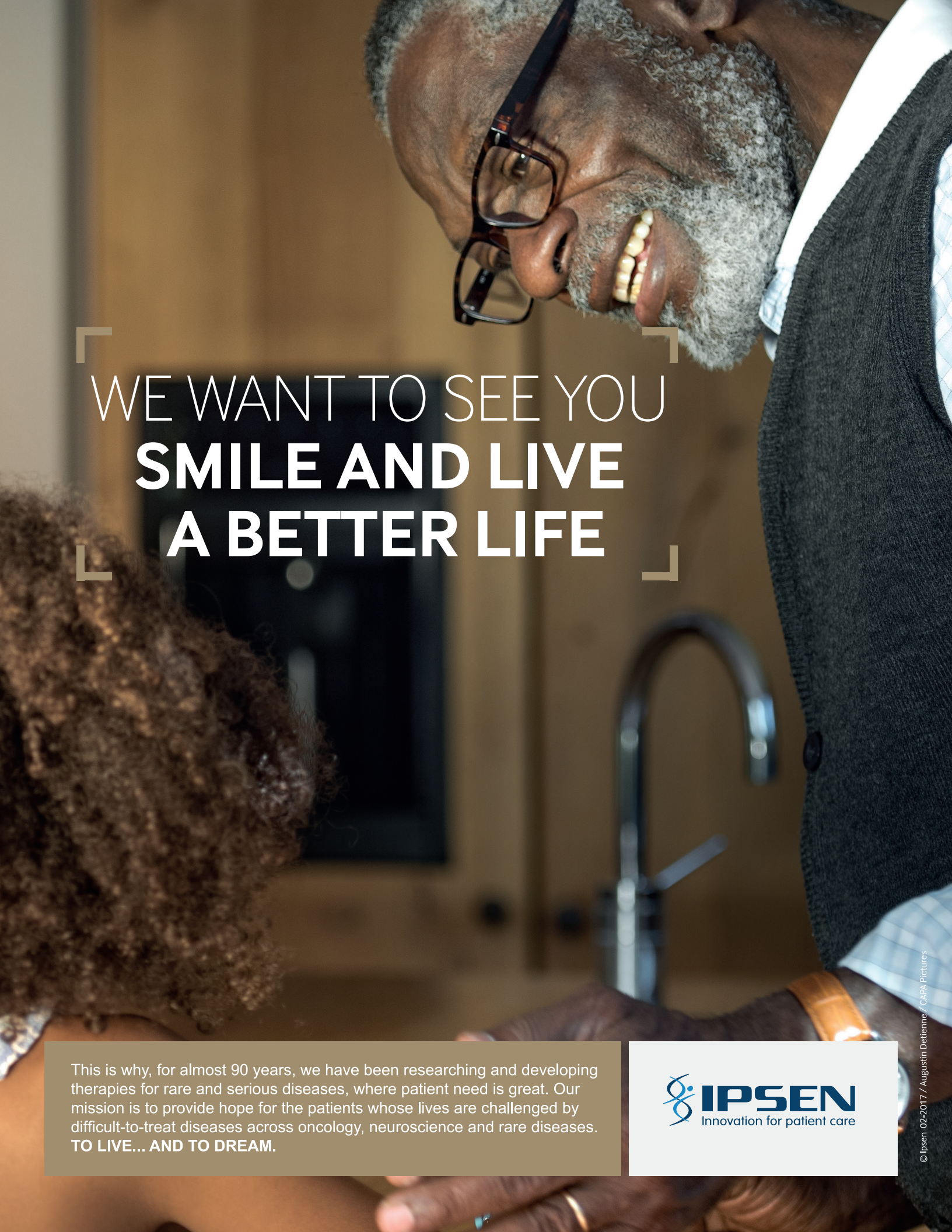
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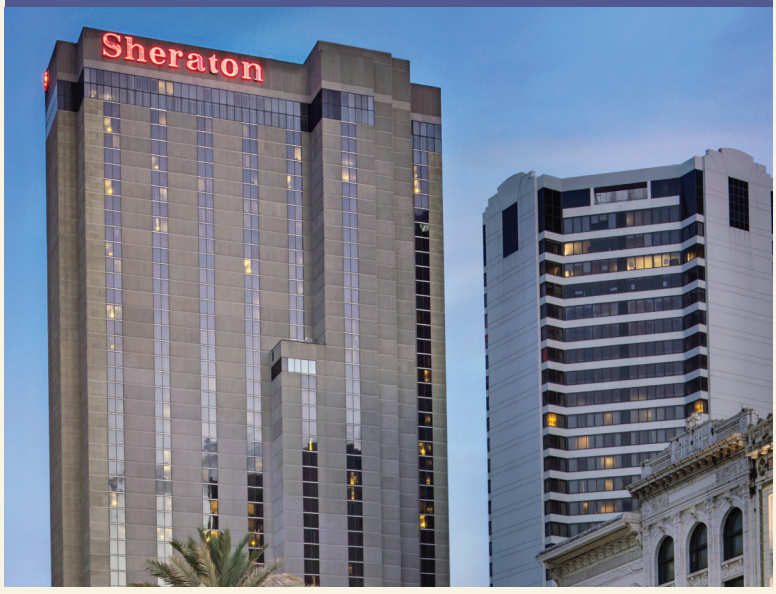

We hope to see you in 2021 in San Diego at the next Pituitary Congress.

Contact info@pituitarysociety.org for more information.