

THE PITUITARY SOCIETY
presents the

12th

TWELFTH
INTERNATIONAL
PITUITARY
CONGRESS

JUNE 1 - 3, 2011

Boston, MA

Immediately preceding ENDO 2011

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PROGRAM AND ABSTRACTS

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Welcome

Dear Colleague,

The 12th International Pituitary Congress will provide an exciting forum for member and guest international experts discussing the latest updates in basic, translational and clinical pituitary medicine. The program includes experienced clinicians and clinical researchers, fellows in training, and experts in basic science. As usual, we will present cutting edge in-depth topics that will permit each attendee to become familiar with the latest trends in pituitary endocrinology. The 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, those selected for Hot Topics and poster presentations. Please note our corporate partners who are providing support for both our educational sessions and social events. We gratefully acknowledge their continued generous support. Welcome again to two days of excellent science and companionship!

The Program Organizing Committee



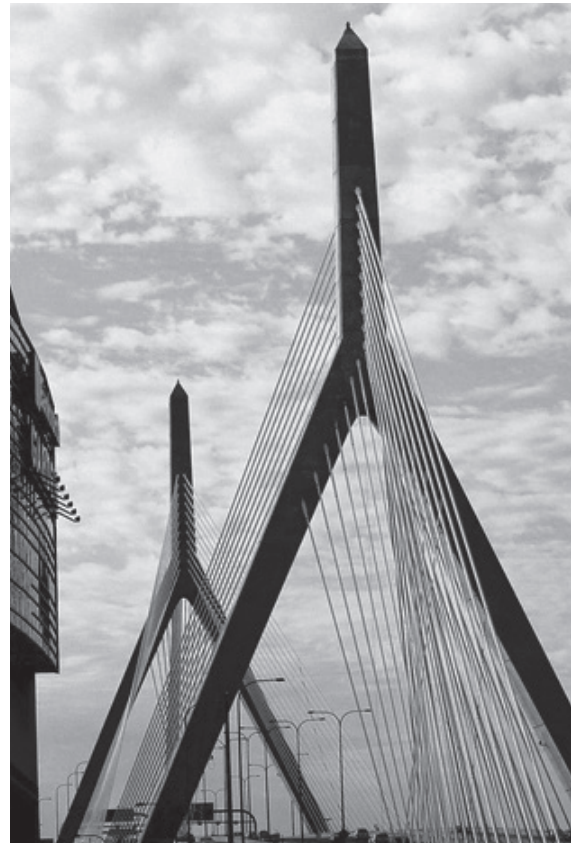
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Symposium Schedule

WEDNESDAY, JUNE 1

7:00 pm	OPENING PLENARY SESSION	
7:15 pm	Clinical Debate: Is cabergoline safe for patients with prolactinomas? <i>Moderator: John A.H. Wass</i>	<i>Annamaria Colao vs. Janet A. Schlechte</i>
8:00 pm	WELCOME RECEPTION - THE FOUR SEASONS HOTEL BOSTON	

THURSDAY, JUNE 2

7:00 am BREAKFAST

I. ACROMEGALY

Chair: Andrea Giustina

8:30 am	Safety and efficacy of oral somatostatin peptide	<i>Sam Teichman</i>
8:50 am	Combined treatment with SRIF analogs and GH receptor antagonist	<i>Sebastian J. Neggers</i>
9:10 am	GH control: GHRH and/or Ghrelin?	<i>Roy G. Smith</i>

II. GENETICS OF PITUITARY TUMORS

Chair: Albert Beckers

9:30 am	Carney complex	<i>Lawrence S. Kirschner</i>
9:50 am	MEN I	<i>Stephen J. Marx</i>
10:10 am	Familial acromegaly	<i>Monica Gadelha</i>
10:30 – 11:00 am	COFFEE BREAK AND POSTER PRESENTATIONS	

III. PITUITARY TUMOR RECURRENCES

Chair: Brooke Swearingen

11:00 am	Pathologic markers	<i>Jacqueline Trouillas</i>
11:20 am	Clinical determinants	<i>Ferdinand Roelfsema</i>
11:40 am	Long-term results of pituitary tumor gamma knife therapy	<i>Jason Patrick Sheehan</i>

MEET THE PROFESSOR CONCURRENT LUNCH WORKSHOPS

12:00 – 1:30 pm	Does GH enhance athletic performance?	<i>Ken Ho</i>
	How to taper steroid therapy?	<i>John Newell-Price</i>
	Small animal pituitary imaging technologies	<i>Iain C. Robinson</i>
	Withdrawal of dopamine agonists	<i>Roberto Salvatori</i>

IV. PITUITARY TUMOR PATHOGENESIS

Chair: Margaret E. Wierman

1:45 pm	Epigenetic mechanisms	<i>William E. Farrell</i>
2:05 pm	Why are pituitary tumors benign?	<i>Vera M. Chesnokova</i>
2:25 pm	Role of MEG3 in pituitary tumorigenesis	<i>Xun Zhang</i>

V. OBESITY AND APPETITE CONTROL

Chair: Felipe F. Casanueva

2:45 pm	Role of melanocortin receptors	<i>Roger Cone</i>
3:00 pm	Endocrine complications of gastric bypass surgery	<i>Lee M. Kaplan</i>

Symposium Schedule

VI. DEBATE

- 3:15 – 3:45 pm Pituitary disease mortality – fact or fiction? *John Ayuk vs. Eva Marie Erfurth*
Moderator: Ashley B. Grossman
- 3:45 – 4:15 pm COFFEE BREAK AND POSTER PRESENTATIONS

VII. HOT TOPICS

Chairs: Paolo Beck-Peccoz and Michael O. Thorner

- 4:15 – 5:15 pm Early medical treatment of pituitary lesions, the Johns Hopkins Experience 1896 to 1912 *Alfredo Quinones-Hinojosa*
- Ablation of POMC neurons induces an obese phenotype characterized by decreased food intake and enhanced anxiety in unstressed mice *Yona Greenman*
- Hypopituitarism in retired professional football players: A prospective study *Daniel Kelly*
- GALA DINNER**
- 6:30 - 7:30 pm COCKTAIL RECEPTION
- 7:30 pm DINNER

FRIDAY, JUNE 3

- 7:00 am BREAKFAST

VIII. CUSHING'S DISEASE

Chair: Beverly M.K. Biller

- 8:30 am Role of adrenal steroid blockers *Lynnette Nieman*
- 8:50 am Mechanisms of hypercortisolemic insulin resistance and obesity *Márta Korbonits*
- 9:10 am SOM230 treatment *Stephan Petersenn*
- 9:30 am – 9:45 am BUSINESS MEETING AND PRESIDENTIAL ADDRESS *Kalman Kovacs*

IX. PITUITARY TUMOR: CHALLENGES

Chair: Kalman Kovacs

- 9:45 am Pituitary tumor surgery *Shozo Yamada*
- 10:00 am Pituitary tumor pathology *Bernd Scheithauer*
- 10:15 am Pituitary tumor pathogenesis *Ricardo Lloyd*
- 10:30 am Pituitary tumor therapy *Luis Syro*
- 10:45 – 11:00 am COFFEE BREAK AND POSTER PRESENTATIONS

X. PITUITARY HORMONE ASSAYS

Chair: Lawrence Frohman

- 11:00 am Is the GH assay valid? *Christian J. Strasburger*
- 11:20 am IGF-I assays - pitfalls *David R. Clemmons*
- 11:40 am Salivary cortisol assays *Hershel Raff*

XI. LUNCHEON AND AWARD PRESENTATION

- 12:00 noon The Novartis Pituitary Society Lifetime Achievement Award
- 1:00 pm Congress Adjourns

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ABSTRACTS
INVITED LECTURES

OPENING PLENARY SESSION

Clinical Debate: Is cabergoline safe for patients with prolactinomas?

Moderator: John A.H. Wass – has no relationships to disclose.

Annamaria Colao – has no relationships to disclose.

Janet Schlechte – has no relationships to disclose.

ACROMEGALY

Chair: Andrea Giustina – receives consulting fees from Ipsen, Novartis and Pfizer and is a speaker for Italfarmaco.

CLINICAL PHARMACOLOGY OF OCTREOLIN™, AN ORALLY BIOAVAILABLE OCTREOTIDE FORMULATION FOR THE TREATMENT OF ACROMEGALY

Sam Teichman, Shmuel Tuvia, Ronit Koren, Jacob Atsmon, Shoshie Katz, Paul Salama, William G. Kramer, Roni Mamluk

Chiasma, Jerusalem, Israel

Background: An orally effective formulation of octreotide would provide improved treatment choices for patients with acromegaly. Octreolin increases oral bioavailability of octreotide to therapeutic levels using a novel Transient Permeability Enhancer (TPE) formulation. TPE facilitates intestinal absorption of the peptide by inducing transient, reversible opening of epithelial cell tight junctions of the small intestine, enabling intact drug absorption. No chemical modification of octreotide was required. Three clinical pharmacology studies with Octreolin have been completed in healthy volunteers.

Objectives: A. To evaluate the pharmacokinetic (PK) profile of octreotide after escalating oral doses of Octreolin. B. To compare PK profiles of oral Octreolin with a SC injection of octreotide. C. To assess the effect of food on octreotide absorption. D. To assess the effect of Octreolin on basal and stimulated growth hormone (GH) secretion. E. To assess the safety and tolerability of Octreolin.

Results: After Octreolin administration, significant oral absorption was achieved within 1 hour. Following doses of Octreolin 3 mg, 10 mg and 20 mg, mean plasma concentrations of octreotide increased dose-dependently with a similar rate of decay, demonstrating linear PK. The PK profile of Octreolin was reproducible in all 3 studies. A dose of Octreolin 20 mg provided similar systemic exposure to octreotide 0.1 mg SC with mean C_{max} (4.1 ± 2.2 vs 6.6 ± 8.9 ng/mL), mean AUC (17.0 ± 9.7 vs 13.7 ± 2.3 h-ng/mL) and median time ≥ 0.5 ng/mL (5.7 vs 4.9 h), all respectively. A single dose of Octreolin significantly suppressed basal mean GH secretion by 83% from 1.6 ± 0.5 to 0.3 ± 0.1 ng/mL and GHRH-stimulated mean GH secretion by 79% from 35.4 ± 3.6 to 8.1 ± 2.4 ng/mL. GH inhibition was observed in all subjects receiving Octreolin. Concomitant food intake significantly reduced systemic absorption of octreotide. Overall, the drug was well tolerated with no significant clinical or laboratory adverse events. Side effects of oral Octreolin were comparable to those of injectable octreotide.

Conclusions: The results of these studies indicate that Octreolin may offer an oral alternative to parenteral somatostatin analog treatment. Larger-scale, efficacy and safety trials in patients with acromegaly are planned.

Sam Teichman, Shmuel Tuvia, Ronit Koren, Shosie Katz, Paul Salama, and Roni Mamluk are employees of Chiasma, Inc. Jacob Atsmon is an investigator for the Clinical Research Center, Tel Aviv Sourasky Medical Center, Israel (payment was made to the Hospital by the sponsor to conduct the clinical trial). William G. Kramer is a consultant for Chiasma, Inc.

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

COMBINED TREATMENT WITH SRIF ANALOGUES AND GH RECEPTOR ANTAGONIST

Sebastian Neggers

Department of Medicine, Section of Endocrinology, Erasmus University Medical Center, Rotterdam, Netherlands

Mono-therapy using long-acting somatostatin analogues and surgery cannot provide optimal biochemical control in a large proportion of patients with acromegaly. This results in increased mortality, poor control of signs and symptoms of disease and decreased quality of life. Combined treatment with somatostatin analogues and pegvisomant (a growth hormone receptor antagonist) seems to be an attractive option. Combination treatment is highly effective at normalising the level of insulin-like growth factor 1 in over 90% of patients and has a favourable effect on quality of life in those with biochemically controlled acromegaly.

With an equal efficacy rate, but at a mean weekly PEG-V dose of 77 mg, long-term combination therapy seems to help reduce the required dose of PEG-V. The magnitude of the decrease can differ greatly between patients. Moreover, combination therapy with somatostatin analogues results in a clinically relevant decrease in tumour size in about 20% of patients, whereas pegvisomant (PEG-V) mono-therapy does not decrease pituitary tumour size. Transient elevations in the levels of transaminases are the main adverse effects of combination treatment, which occur in about 11–15% of patients.

Sebastian Neggers is a speaker for Ipsen, Novartis, and Pfizer.

GH CONTROL: GHRH AND/OR GHRELIN

Roy G. Smith

Department of Metabolism and Aging, The Scripps Research Institute Florida, Jupiter, FL

Based on determining the mechanism of action of synthetic GH secreting peptides identified by Momany and Bowers, small molecule non-peptide mimetics were developed called growth hormone secretagogues (GHS). An orally active compound, MK-0677, that restored amplitude of episodic GH release in elderly subjects to that of young adults was used to express clone the orphan receptor involved (GHSR1a). GHSR1a was subsequently deorphanized by Kojima and coworkers who characterized an endogenous agonist called ghrelin. GHSR1a agonists increase GH pulse amplitude by: activating GHSR1a on hypothalamic GHRH neurons, augmenting GHRH-induced GH release through GHSR1a on somatotrophs, antagonizing the suppressive effect of somatostatin (SST) on GHRH-induced GH secretion from somatotrophs. The role of GHSR1a on GHRH action is fundamentally important because *ghsr*^{-/-} mice exhibit reduced expression of *pit1* associated with modest reductions in somatotrophs and lactotrophs in the anterior pituitary gland. Compared to wild-type mice, *ghsr1a*^{-/-} mice exhibit 20% lower circulating IGF-1 levels and are slightly smaller. Hence, ghrelin and GHRH are intimately involved in the normal regulation of GH release and the absence of either signaling pathway results in impaired GH secretion. From a clinical perspective, provided the subject an intact hypothalamic/pituitary axis, treating GH-deficiency with a long-acting ghrelin mimetic rather than GHRH, would be preferable because the ghrelin mimetic would not bypass normal GH regulatory feed-back pathways.

GH release from somatotrophs is inhibited by SST action mediated through somatostatin receptor subtype-5 (SST5) and subtype-2 (SST2). FRET studies have shown that SST5 signal transduction requires SST-induced formation of SST5:SST5 homomers. However, in the presence of GHSR1a, we show by BRET analysis that SST5 constitutively forms GHSR1a:SST5 heteromers, thereby inhibiting SST action. Intriguingly, formation of heteromers is stabilized by ghrelin and destabilized by high concentrations of SST. High GH causes [SST] to increase providing negative feedback, and when GH is low, [SST] is low. We propose that the relative concentrations of ghrelin and SST establish an equilibrium between GHSR1a:SST5 and SST5:SST5, which finely control GH release by buffering the inhibitory action of SST. Indeed, this model is consistent with the results of studies to determine the concentration dependence of SST inhibition of GHRH-induced GH release in the presence of a GHSR1a agonist. Consistent with our equilibrium model, the presence of a GHSR1a agonist produced a rightward shift in the SST inhibition curve.

We gratefully acknowledge the support of the NIH: R01AG019230.

Roy Smith has no relationships to disclose.

GENETICS OF PITUITARY TUMORS

Chair: Albert Beckers – has no relationships to disclose.

CARNEY COMPLEX: A MODEL FOR PKA-ASSOCIATED INHERITED PITUITARY TUMORS

Lawrence S. Kirschner, MD, PhD

Department of Endocrinology, Diabetes, and Metabolism, Department of Medicine

Department of Molecular Virology, Immunology, and Medical Genetics, The Ohio State University, Columbus, OH

Carney Complex (CNC) is an inherited tumor predisposition associated with spotty skin pigmentation, generalized myxomatosis, endocrine overactivity, and pigmented schwannomas. Pituitary tumors are observed in about 10% of CNC patients, with most of these tumors identified as growth hormone (GH) producing pituitary adenomas, although Prolactin (PRL) co-secretion is common. Frank prolactinomas appear to be rare in this syndrome. At the molecular level, most cases of the disease are caused by inactivating mutations in PRKAR1A, which encodes the type 1A regulatory subunit of the cAMP-dependent Protein Kinase, PKA. Although patients with CNC are heterozygous for the mutation, mounting evidence suggests that total loss is necessary for tumorigenesis. Loss of the normal allele has been documented in a small number of CNC-associated pituitary tumors, whereas other tumors appear to exhibit non-genomic mechanisms causing absence of protein expression. These observations are supported by data from mice, which require complete knockout of the gene in pituitary cells to generate GH-secreting adenomas. At the biochemical level, loss of PRKAR1A causes enhanced PKA signaling, leading both to somatotroph cell proliferation and hormone hypersecretion. The predisposition for mutation in PRKAR1A/Prkar1a to cause acromegaly appears to be related to the signaling pathways employed in specific pituitary cell types. In sum, these data indicate that complete loss of Prkar1a/PRKAR1A is able to cause GH-secreting pituitary tumors in mice and men.

Lawrence Kirschner, MD, PhD is a speaker for Ipsen.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1)

Stephen J. Marx

Metabolic Diseases Branch, NIDDK/NIH, Bethesda, MD

MEN1 is the most heterogeneous of all tumor syndromes, affecting thirty tissues. Its most frequent endocrine tumors in adults are parathyroid (95%), pancreatico-duodenal (50%), and pituitary (40%); the definition of MEN1 is tumor in two of those three main tissues, and familial MEN1 includes a relative with one main tumor. Aggressive pituitary tumor has been seen before age 5 in MEN1, justifying early screening in families. A mouse model suggests that MEN1 islet tumors begin with polyclonal hyperplasia. Multiplicity of tumors occurs in the more frequently affected tissues, but not the pituitary. Germline mutation of MEN1 is identifiable in 70% of kindreds. Somatic MEN1 mutation occurs in 30% of common tumors of the parathyroids or pancreatico-duodenum, but only 3% of common pituitary tumors. Probably, mutations of other genes cause most common pituitary tumors. The prolactinoma or Burin variant of MEN1 has been reported in three families with 13-90 affected members. Large family size has been essential for recognition of this variant; its variations from typical MEN1 include more frequent prolactinoma (60%) and much less frequent gastrinoma (5%). Their three different MEN1 mutations seem similar to typical MEN1. An interesting subgroup with "MEN1" expresses sporadic tumor only of the pituitary and parathyroid. MEN1 mutation has been rare (7%) therein, indicating a different cause usually. For a spectrum of MEN1 cases and MEN1-like cases without identified MEN1 mutation, mutations in other genes have been sought. Mutation was implicated occasionally in four cyclin dependent kinase inhibitor (CDKI) genes: p15, p18, p21, and p27; MEN1 with p27 mutation was termed MEN4 by OMIM. The phenotype in ten small kindreds with CDKI mutation is MEN1-like including isolated hyperparathyroidism. CDKI genes warrant exploration for somatic mutation in common pituitary tumors.

Stephen J. Marx has no relationships to disclose.

FAMILIAL ACROMEGALY

Monica Gadelha

HUCFF-UFRJ, Rio de Janeiro, Brazil

The spectrum of familial acromegaly has increased over the past decade to include syndromes associated with multiple endocrine tumors (multiple endocrine neoplasia types 1 and 4; Carney complex) and families with isolated pituitary adenomas (Familial Isolated Pituitary Adenomas - FIPA) of which isolated familial somatotropinomas (IFS) constitute the largest subgroup.

In 2000, we established that a tumor suppressor gene (TSG) located at chromosome 11q13 was involved in the pathogenesis of IFS. Vierimaa et al. found germline mutations in a gene located at this chromosome region, the aryl hydrocarbon receptor interacting protein (AIP) gene, in two Finnish families with FIPA. Leontiou et al. demonstrated that the AIP gene has indeed properties consistent with a TSG. AIP mutations are found in approximately 50% of IFS families but in less than 30% of FIPA families.

Patients harboring AIP mutations are usually younger at the time of diagnosis than those without a mutation. In addition, patients with AIP mutations frequently present a more aggressive disease, with invasive adenomas, and have a low chance of surgical cure and a poor response to available medical treatments, such as somatostatin analogues in acromegaly.

The establishment of the molecular basis of inherited neoplastic diseases, in addition to allowing genetic counseling, contributes to the comprehension of the pathogenesis of the sporadic neoplasias, which are responsible for the vast majority of the tumors. Therefore, to investigate the role of AIP in sporadic somatotropinoma tumorigenesis, we studied a series of 38 adenomas (23 invasive) by immunohistochemistry. Cytoplasmic AIP immunostaining was detected in 100% of the somatotropinomas but lower AIP immunostaining was detected in invasive versus non-invasive cases, suggesting that decreased AIP expression may be involved in the pathogenesis (tumor progression) of sporadic somatotropinomas. In addition, this finding suggests that AIP immunostaining may be used as a marker of tumor invasiveness, what holds enormous clinical relevance.

Monica Gadelha has no relationships to disclose.

PITUITARY TUMOR RECURRENCES

Chair: Brooke Swearingen – has no relationships to disclose.

PATHOLOGIC MARKERS OF RECURRENCE IN PROLACTIN PITUITARY TUMORS

J. Trouillas PhD, MD

INSERM, U1028, Lyon Neuroscience Research Center, Neuro-Oncology-Neuro-Inflammation Team, Lyon; University Lyon 1, Villeurbanne; CPE, GPE Bron, F-69000, France

The prediction of pituitary tumor behaviour remains a challenge. In pathological studies, increased levels of mitotic, Ki-67, proliferation cell nuclear antigen, and P53 indexes have been found in invasive tumors, as well as expression of polysialic acid neural cell adhesion molecule and overexpression of pituitary transforming tumor gene (PTTG). The results conflict from one series to another and the limited usefulness of these markers is probably due to the criteria of invasiveness and the existence of several tumoral cell phenotypes. Moreover, these markers have not yet been correlated with postoperative results and recurrence in clinical studies.

To identify such markers, we conducted a multiparameter investigation in a cohort of 94 patients treated for prolactin tumors by surgery, with a long post-operative follow-up period. We retrospectively studied clinical data, tumor characteristics, the expression of 9 genes by q-RT-PCR and chromosomal alterations by comparative genomic hybridization.

Tumors were classified into 3 pathological groups (non-invasive, invasive and aggressive-invasive) based on their radiological and histological characteristics. Sixty patients (63%) went into remission immediately after surgery. An early negative outcome was associated with increasing age, male sex, high preoperative prolactin levels, large tumor size on univariate analysis and invasion and pathological classification on univariate and multivariate analysis. During follow-up, 21 % of the tumors recurred. Invasion, pathological classification and expression of 7 genes (ADAMTS6, CRMP1, PTTG, ASK, CCNB1, AURKB, CENPE) were associated with recurrence. Moreover, allelic loss within the p arm region of chromosome 11 was detected in 5 out of 6 aggressive-invasive tumors with recurrence. Allelic loss in the 11q arm was observed in three of them, considered as malignant based on the occurrence of metastases.

Clinical, histological, molecular and genomic markers relating to prolactin tumor recurrence could influence the management of patients with pituitary tumors.

J. Trouillas, PhD, MD has no relationships to disclose.

CLINICAL DETERMINANTS OF PITUITARY TUMOR RECURRENCES

Ferdinand Roelfsema, Nienke R. Biermasz, Alberto M. Pereira

Department of Endocrinology, Leiden University Medical Center, Leiden, The Netherlands

The incidence of recurrence after surgical cure of pituitary adenomas and the associated promoting factors are not precisely known. We therefore undertook a systematic review by searching Medline, Embase, Web of Science and the Cochran Library for studies reporting recurrence of pituitary adenoma after surgery. In total, 556 potential relevant studies reporting surgical outcome of NFA, prolactinoma and M. Cushing were selected. After reading the abstract or in case of doubt the full article 98 publications were used for evaluation. Recurrence was defined as growth and/or increase of hormone levels above normal limits as set by the authors. Recurrence, expressed as percentage of the cured population (median and range) was: NFA 11.3% (0-56), prolactinoma 16.4% (0-61), and M. Cushing 11.2% (0-55), ANOVA P=0.219. Expressed as recurrence number per total patient years of follow-up: NFA 0.024 (0-0.108), prolactinoma 0.035 (0-0.187), and M. Cushing 0.024 (0-0.106), ANOVA, P=0.025. Most of the studies with a sufficient number of recurrences did not apply multivariate statistics, and mentioned at best associated factors. Age, gender, and tumor size were generally unrelated to recurrence, while tumor invasiveness was related to recurrence in about half of the studies. For prolactinoma a low postoperative prolactin level (3-10 ng/mL) and a low or immeasurable cortisol concentration in M. Cushing were prognostically favorable factors. These results are compatible with the hypothesis that tumor recurrence is outgrowth of tiny tumor remnants. We are currently evaluating whether these results also apply for acromegaly.

None of the authors have any relationships to disclose.

LONG-TERM RESULTS OF PITUITARY TUMOR GAMMA KNIFE RADIOSURGERY

Jason Sheehan, MD, PhD

University of Virginia, Charlottesville, VA

Introduction: Secretory and nonsecretory pituitary adenomas can recur after microsurgery. Various forms of radiation therapy and radiosurgery have been used to treat recurrent pituitary adenomas. Gamma Knife surgery (GKS) is one of the most commonly utilized forms of radiosurgery in the modern era.

Methods: This presentation details the long term rates of tumor control and endocrine remission afforded by GKS for the major cohorts of pituitary adenoma patients. Complications such as hypopituitarism and other more rare ones are discussed.

Results: GKS yields a high rate of tumor control (90% or higher) in most series regardless of adenoma subtype. Endocrine normalization after GKS varies significantly across series. The variability is dependent upon patient selection, radiosurgical technique, definition of endocrine success, and length of follow up. Overall, endocrine remission is achieved in >50% of patients post-GKS. Endocrine remission is improved in patients with lower tumor volumes and those for whom a temporary cessation of antiseecretory medications was performed at the time of radiosurgery. Hypopituitarism occurs in 30% of patients. Rates of other radiosurgical induced complications are very low.

Conclusions: GKS resulted in a high and durable rate of tumor control in patients with a recurrent pituitary adenoma. It also delivers a reasonable rate of endocrine normalization. Long-term and multidisciplinary follow up is required to detect delayed recurrences or hypopituitarism.

Jason Sheehan, MD, PhD has no relationships to disclose.

MEET THE PROFESSOR CONCURRENT LUNCH WORKSHOPS

DOES GROWTH HORMONE ENHANCE ATHLETIC PERFORMANCE?

Ken Ho

Centres for Health Research, Princess Alexandra Hospital and University of Queensland, Brisbane, Australia

Human growth hormone (GH) is widely abused by athletes, however there is little evidence that GH improves physical performance. GH deficiency presents with low muscle mass and impaired physical performance. Replacement of GH in GH deficiency improves some aspects of exercise capacity. There is evidence for a protein anabolic effect of GH in healthy adults and for increased lean body mass following GH, although fluid retention likely contributes to this increase. Despite the large doses used, there is little evidence that GH enhances physical performance in healthy adults or in trained athletes. The latest evidence from a large placebo-controlled trial in recreational athletes show that GH enhance anaerobic exercise capacity but not muscle strength, power, or aerobic exercise capacity. There are, however, risks of adverse effects of long-term abuse of GH. These include oedema, carpal tunnel syndrome, arthralgias, myalgias, insulin resistance, diabetes, cardiomyopathy and possibly malignancy.

Supported by the NHMRC of Australia and the World AntiDoping Agency.

Ken Ho is on an advisory committee for Lilly and is a speaker for Novo Nordisk.

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

HOW TO TAPER STEROID THERAPY?

John Newell-Price

University of Sheffield, UK

Endocrinologists frequently have to reduce doses of glucocorticoids in patients with adrenal insufficiency who have had the doses transiently increased because of intercurrent illness, and also in patients who have been treated for Cushing's syndrome. In addition we are often called upon for advice about reducing doses in patients who have received these steroids because of inflammatory disease but where the underlying inflammatory condition has resolved. There is a dearth of 'evidence' in this area but a wealth of clinical experience, and endocrine practice, based on clear physiological principles. Monitoring of the tapering process, and activity of the HPA axis, may be made on clinical grounds as well as monitoring of early morning serum cortisol and plasma ACTH, in addition to stimulatory tests, including the ACTH stimulation test. Recovery of a long-term glucocorticoid-suppressed HPA axis in patients in whom there will be adrenal atrophy is characterized by a gradual recovery of plasma ACTH levels, that then become supra-normal, followed then by a sufficient response to ACTH-stimulation testing. This knowledge may be used as guide as to where a given individual is on the 'road to axis recovery', and this information then placed in the clinical context of their symptoms and signs, allowing rational advice to be given during the tapering process.

This workshop will address these issues, with discussion of illustrated cases in clinical situations including:

- 1) Tapering of steroids in patients on glucocorticoid replacement regimes after a transient increase for intercurrent illness.
- 2) Tapering of steroids in patients with Cushing's syndrome following successful intervention.
- 3) Tapering of steroids in patients on glucocorticoids for inflammatory purposes.

John Newell-Price has no relationships to disclose.

SMALL ANIMAL PITUITARY IMAGING

ICAF Robinson

MRC National Institute for Medical Research, London, UK

Recent years have seen significant advances in direct imaging technologies applied to small animals, including visible, infrared, fluorescence or bioluminescence microscopy, which can reveal cellular or even subcellular events in real time. Progress has also been made in adapting some indirect techniques used in human or veterinary medicine, such as MRI/PET/CT and ultrasound though these require significant investment in equipment and infrastructure, and at present do not offer the resolution available with direct microscopic techniques. Imaging the pituitary gland in experimental animals poses problems due to its small size, complex structure and relative inaccessibility within the sella turcica. However, by using transgenic techniques, one can express fluorescent proteins of different colours in specific pituitary cell populations in mice or rats. Combining this with a surgical approach to expose the gland surface in situ, it is possible to image single cells and populations of pituitary cells in these transgenic animals, using long working-distance objectives for stereo fluorescence microscopy, and/or multi-photon techniques. Image processing and reconstruction techniques capture the entire population of specific hormone cell types, revealing their 3-D network organisation within the normal gland, and how this alters in pathophysiological states. Calcium imaging can reveal activity of identified pituitary cell types during secretory events, whilst intravascular or intra-parenchymal injections of fluorescent dyes allows the measurement of pituitary or portal blood flow, as well as the kinetics of secretagogue entry into, and secretory protein exit from, the intact gland. By targeting the transgene fluorophore to secretory vesicles (SVs) and using TIRF microscopy, it is possible to image individual SVs to study and quantify pituitary hormone release events. New developments in optogenetics now allow us to turn cell activity on and off using different wavelengths of light, and these will open up new ways to understand how pituitary cell networks function.

ICAF Robinson has no relationships to disclose.

WITHDRAWAL OF DOPAMINE AGONIST THERAPY

Roberto Salvatori, MD

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Dopaminergic agents (DAs) are the main treatment for prolactinomas. Cabergoline (CAB) is more effective and better tolerated than bromocriptine (BRC). CAB is able to normalize serum prolactin in excess of 90% of patients, and to cause significant tumor shrinkage in a large percentage of them. New concerns were raised by the observation that CAB and pergolide, at high doses used in Parkinson's disease, may cause heart valve damage. While the current literature does not seem to support the concept that the dosages commonly used to treat prolactinomas pose significant risk, it is reasonable to use the lowest and shortest possible effective dose. In the past it had been recognized that some microprolactinoma disappear spontaneously (or after pregnancy or at the time of menopause). However, in most cases dopaminergic therapy was considered a lifetime treatment. A landmark study by Colao et al. in 2003 showed that a subset of patients (with macro- and micro-prolactinomas and idiopathic hyperprolactinemia) can be permanently cured by CAB. The criteria for CAB withdrawal were a minimum of 2 years of treatment, tumor shrinkage, and control by a minimal dosage. The highest remission rate was reported in patients who had tumor disappearance after CAB treatment. This study has been followed up by others that have confirmed that a subset of patients can permanently stop CAB, although the recurrence rates have been higher than in the Colao's report. A recent meta-analysis has shown less promising data, with recurrence rate of 79% after DA therapy, although most studies included patients treated with BRC. It is important to notice that DA withdrawal is safe even in patients who relapse, as serum prolactin increase occurs before any detectable and clinically significant tumor growth. These data prompted the Pituitary Society to formulate guidelines recommending that dopamine agonists can be safely withdrawn in [normoprolactinemic] patients with no evidence of tumor on MRI" and that "a trial of tapering and discontinuation if the tumor volume is markedly reduced". Using these guidelines, the average risk of long-term recurrence is approximately 60%. The median time to recurrence is 3 months, with 91% of recurrences occurring within 1 yr after CAB discontinuation. Size of tumor remnant prior to withdrawal predicted recurrence (18% increase in risk for each mm). Therefore, close follow-up remains important, especially within the first year after withdrawal. Important yet unanswered questions remain, such as whether longer treatments reduce the risk of recurrence, and whether a second withdrawal attempt after a failure has a chance to be successful.

Roberto Salvatori, MD has no relationships to disclose.

PITUITARY TUMOR PATHOGENESIS

Chair: Margaret Wierman – has no relationships to disclose.

EPIGENETICS OF PITUITARY TUMORS

William E. Farrell

ISTM, University of Keele, UK

In marked contrast to the genetic aberration, that characterise most tumour types, these types of change are infrequent in pituitary adenomas. With noted and particular exceptions the underlying mechanisms responsible for inappropriate expression of developmental, cell-cycle regulatory and apoptotic genes have not thus far been defined. However, and in common with other tumour types pituitary adenomas harbour multiple epigenetic aberrations. These changes, imposed post-replication, are responsible for loss or significantly reduced expression of gene-specific products that in some cases are subtype specific. Principle epigenetic changes include methylation of promoter-associated CpG islands and histone tail modifications. These modifications, acting either independently or in concert contribute toward gene silencing. Several studies have adopted candidate gene approaches and more recently whole genome analyses and their importance in the context of pituitary tumourigenesis will be reviewed. Other, still more recent investigations, have exploited “pharmacological unmasking” to reverse epigenetic gene silencing to “uncover” silent genes. These types of studies have led to their investigation as potential adjuncts to clinical management strategies. We have used pharmacological unmasking to explore the epigenetic profile of the dopamine D2 receptor (D2R). In a pituitary tumour cell line model our studies showed, that loss D2R is associated with an increase in promoter-associated CpG island methylation that is also accompanied by enrichment for a histone mark associated with gene silencing, H3K27me3. Co-culture of GH3 cells, with a demethylating agent and a histone deacetylase inhibitor, led to decrease in CpG island methylation and concomitant enrichment for a histone mark associated with active genes, H3K9Ac. The “unmasking” led to re-expression of endogenous D2R in these cells and an associated significant, and specific, increase in apoptosis indices to challenge with either Dopamine or its analogue Bromocriptine, and point to the potential use of combined treatment with epigenetic drugs and dopamine agonists for the medical management of different pituitary tumour subtypes, resistant to conventional therapies.

William Farrell has no relationships to disclose.

WHY ARE PITUITARY TUMORS BENIGN?

Vera Chesnokova

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As pituitary adenomas are invariably benign, we studied unique trophic mechanisms underlying the restraint of pituitary cell proliferation. Human GH-secreting adenomas exhibit aneuploidy, DNA damage and expression of Cdk inhibitor p21 that leads to proliferation restraint and cellular senescence evident in these tumors. We also tested mechanisms constraining non-functioning pituitary adenoma growth. Thirty six gonadotroph-derived non-functioning pituitary adenomas all exhibited DNA damage, but undetectable p21 expression. In contrast to GH adenomas, these adenomas all expressed p16, and >90% abundantly expressed cytoplasmic clusterin associated with induction of the Cdk inhibitor p15 in 70% of gonadotroph and in 26% of somatotroph lineage adenomas (p= 0.006). Murine L β T2 and α T3 gonadotroph pituitary cells, and α GSU.PTTG transgenic mice with targeted gonadotroph cell adenomas also abundantly expressed clusterin and exhibited features of premature cell cycle arrest and oncogene-induced senescence as evidenced by C/EBP β and C/EBP δ induction. In turn, C/EBPs activated the clusterin promoter ~5 fold, and the elevated clusterin subsequently elicited p15 and p16 expression, acting to arrest murine gonadotroph cell proliferation. In contrast, specific clusterin suppression by induced RNAis resulted in enhanced gonadotroph cell proliferation. FOXL2, a tissue-specific gonadotroph lineage factor, also induced the clusterin promoter ~3 fold in α T3 pituitary cells, further confirming the cell specificity of these trophic patterns. As nine of 12 pituitary carcinomas were devoid of clusterin expression, this protein may limit proliferation of benign adenomatous pituitary cells. These results point to lineage-specific pathways restricting uncontrolled murine and human pituitary gonadotroph adenoma cell growth.

Vera Chesnokova has no relationships to disclose.

ROLE OF MEG3 IN PITUITARY TUMORIGENESIS

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The molecular mechanisms for the pathogenesis of human clinically non-functioning pituitary tumors remain elusive. MEG3 is an imprinted gene with maternal expression located on human chromosome 14q32, a location suggested to harbor a tumor suppressor. We have found that MEG3 is highly expressed in all types of cells in the normal human anterior pituitary. In contrast, loss of MEG3 is found exclusively in human clinically non-functioning pituitary tumors. Therefore, MEG3 represents the first human gene identified to be specifically associated with clinically non-functioning pituitary tumors. Functionally, MEG3 suppresses in vitro cell growth and in vivo tumor formation, increases protein expression of the tumor suppressor p53, and selectively activates p53 target genes. Knockout of the MEG3 counterpart in mice resulted in perinatal death, a phenomenon commonly observed with the knockout of tumor suppressor genes. However, unlike most tumor suppressors, MEG3 does not encode a protein. Instead, its gene product is a large non-coding RNA. Using computer modeling combined with functional assays, we have found that correct RNA folding structures within MEG3 RNA are critical for its functions, and different folding structures are involved in different biological functions. Therefore, our studies have revealed novel mechanisms for the function of a large non-coding RNA in pituitary tumorigenesis.

Xun Zhang, PhD has no relationships to disclose.

OBESITY AND APPETITE CONTROL

Chair: Felipe Casanueva – receives consulting fees from Pfizer and Boehringer Ingelheim and is a speaker for Pfizer.

Lee M. Kaplan is a Consultant for GI Dynamics.

AGOUTI RELATED PROTEIN EXPRESSING NEURONS PROJECT TO THE PITUITARY AND REGULATE GROWTH HORMONE EXPRESSION IN A TELEOST

Chao Zhang^{1,2}, Paul M. Forlano³, Roger D. Cone²

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Haploinsufficiency of the melanocortin-4 receptor (MC4R) in humans not only causes morbid obesity, but also causes increased linear growth and final height, relative to control obese subjects. This increase in length is found in zebrafish with defective MC4R signaling as well. Like mammals, zebrafish MC4R activity is modulated by endogenous agonist MSH (melanocyte stimulating hormone) and antagonist AgRP (Agouti-related Protein), respectively. Using antisense morpholino oligonucleotides (MO) to block early gene expression, we report that inhibition of MC4R signaling by endogenous AgRP is required for normal somatic growth in larval zebrafish. MO designed to block AgRP expression, but not MO against agouti, reduce the length of larval zebrafish by up to 25% at 5 days post fertilization, without decreasing the number of somites. The mechanism by which melanocortin signaling regulates somatic growth in mammals has not yet been elucidated. In teleosts, we show that hypothalamic MSH and AgRP fibers project to the anterior pituitary and directly regulate expression of several pituitary genes, including growth hormone, in an MC4R dependent manner. GH mRNA is decreased several fold in AgRP MO but not control treated zebrafish larvae. A compensatory increase in hypothalamic ghrh (growth hormone releasing hormone) and decrease in two sst (somatostatin) genes suggest the primary defect is in pituitary gh expression. These studies elucidate a mechanism by which central melanocortin signaling regulates somatic growth in a teleost.

None of the authors have any relationships to disclose.

DEBATE: PITUITARY DISEASE MORTALITY – FACT OR FICTION?

Moderator: Ashley Grossman – has no relationships to disclose.

John Ayuk – is a member of advisory committees for Ipsen, Novartis and Otsuka.

PITUITARY DISEASE MORTALITY - FICTION?

Eva Marie Erfurth

Skånes University Hospital, Lund University, Lund, Sweden

During the last 20 years a tremendous improvement in the care of patients with pituitary tumors has been achieved. After resolving most of the causes to the much increased cerebro- and cardiovascular mortality a normal survival is expected in these patients. Recently, a large population based study showed a decline in the risk of non-fatal stroke and of non-fatal cardiac events in GH deficient patients. This improvement was achieved by GH replacement and by sufficient other hormone replacement, together with prescription of cardio protective drugs. If we follow the latest achievements in pituitary imaging, surgery techniques, hormone substitutions, cardio protective medications, and if we use available modern therapies for functioning pituitary adenomas no increase in cardiovascular or in all cause mortality is expected in these patients.

Eva Marie Erfurth is a member of an advisory board for Eli Lilly.

CUSHING'S DISEASE

Chair: Beverly MK Biller – has no relationships to disclose.

CUSHING'S DISEASE: ROLE OF ADRENAL STEROID BLOCKERS

Lynnette Nieman

National Institutes of Health, Bethesda, MD

Medical therapy to inhibit adrenal steroidogenesis is most often used as adjunctive treatment until radiotherapy is effective. As monotherapy, unless ablative doses of mitotane are used, hypercortisolism recurs when medication is discontinued. Thus, monotherapy is a life-long commitment. Ketoconazole, metyrapone and mitotane are used. Not all are available world-wide and some are not officially recognized for this indication. Daily doses are generally no more than 2g. Ketoconazole is well tolerated and effective in up to 40% of patients as monotherapy. However, it carries a very small risk (1:10,000) of hepatic dyscrasia, so that liver enzymes must be monitored and the agent stopped if they increase more than three-fold normal. Metyrapone controls hypercortisolemia in 80%. Anecdotally, side effects increase out of proportion to increased efficacy at a daily dose of more than 2g. Increased androgenic precursors may cause hirsutism in women and increased mineralocorticoids may cause hypertension, hypokalemia and edema. o,p'DDD (mitotane) is cytotoxic at high doses and inhibits cortisol synthesis at lower doses. It is stored in adipose, with a slow onset of action and a long half-life. Concomitant food ingestion mitigates gastrointestinal side effects. At doses > 2 g neurologic toxicity reduces tolerability. Teratogenicity limits its use in women desiring fertility in the near future. Gastrointestinal complaints occur with each agent. Ketoconazole and metyrapone combinations are used for patients with ectopic ACTH secretion, but have not been described in Cushing's disease. Variability of cortisol production is maintained (at lower levels) with medical treatment. High variability may result in adrenal insufficiency on some days, and hypercortisolemia on others. A "block and replace" strategy in which cortisol is decreased nearly to zero, and glucocorticoid replacement is given, may be necessary in these patients, while others can be blocked to a normal target morning cortisol (except for mitotane) and/or UFC.

Lynnette Nieman has no relationships to disclose.

CUSHING'S SYNDROME - MECHANISMS OF INSULIN RESISTANCE AND OBESITY

Marta Korbonits¹, Csaba Fekete², Miski Scerif¹, Ashley B. Grossman¹, Blerina Kola¹

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The adrenal cortex steroid hormone glucocorticoids received their name as they regulate glucose metabolism (glucose + cortex + steroid). They stimulate liver glucose output and reduce glucose uptake by some tissues. Glucocorticoids and insulin have opposite or synergistic effects depending on the tissue and metabolic (fasting or feeding) context. For example central glucocorticoids increase food intake while central insulin inhibits food intake. In the liver they synergise to stimulate glycogenogenesis and most recently they were shown to stimulate insulin action in human adipocytes. Elucidation of the pathways involved is hindered by the fact the humans and rodents may respond differently to glucocorticoid excess or deficiency.

Glucocorticoids regulate a number of processes which are also influenced by the metabolic enzyme AMPK. We have hypothesised that glucocorticoids could influence AMPK activity. In a rat model of glucocorticoid excess combined with high carbohydrate intake-induced hyperinsulinaemia we established that glucocorticoids induce hypothalamic AMPK activity and this also correspond to high hypothalamic endocannabinoid content. These data were also confirmed in in vitro studies. In the periphery cardiac and fat tissue showed reduced basal AMPK activity, while liver tissue showed increased AMPK response, again corresponding to in vitro results. To further explore the possible involvement of the endocannabinoid pathway we studied our Cushing's syndrome model in CB1-knockout animals and established that endocannabinoids are involved in the hypothalamic effects and possibly liver effects but not the fat tissue effects.

None of the authors have any relationships to disclose.

TREATMENT WITH SOM230 IN PATIENTS WITH CUSHING'S DISEASE

Stephan Petersenn

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Because established therapies for Cushing's disease - surgery and radiation - are not consistently successful and have limitations with respect to efficacy and side effects, there is a need for an effective medical treatment. Interestingly, corticotrophic pituitary adenomas have been demonstrated to express multiple somatostatin receptor subtypes, with especially high levels of sst5.

Pasireotide (SOM230) is a recently developed multi-receptor ligand somatostatin analog. It exhibits a 20-30 times higher binding affinity to sst1, a 5 times higher affinity for sst3, and a 40-100 times higher binding affinity to sst5, when compared to octreotide and lanreotide. In primary cultures of corticotrophic pituitary adenomas, pasireotide inhibited ACTH secretion and cell proliferation. Furthermore, pasireotide inhibited CRH-induced ACTH-release and corticosterone levels in rats.

In a phase II, proof-of-concept, open-label, single-arm, multicenter study, the in-vivo efficacy of pasireotide was evaluated in patients with Cushing's disease (1). After 15 days of pasireotide 600 µg sc twice daily, UFC decreased significantly by 44.5%. Normalization of UFC was found in 17% (5/29) of patients. Reported side effects resembled those known for somatostatin analogues, except for an increased rate of hyperglycemia (36%). More recently, the preliminary results of a phase III, randomized, double-blind, multicenter trial were presented (2). 162 patients with active Cushing's disease were randomized to receive pasireotide 600µg or 900µg subcutaneously bid for 12 months. 14.6% and 26.3% for the 600 µg and 900µg doses, respectively, normalized UFC at 6 months without dose up-titration relative to the randomized dose. There was a reduction in median UFC at 12mo of -67.6% (600µg) and -62.4% (900µg). Both groups included mainly patients with severe disease, as indicated by the mean basal activity of 8.0x ULN and 5.4x ULN, respectively. A lack of response could be identified within 2 months in the vast majority of patients. The most frequently reported adverse events were diarrhea (58.0%), nausea (51.9%), and hyperglycemia (40.1%). Fasting glucose and HBA1C levels were significantly increased during treatment. Pasireotide has also been studied in a stepwise combination approach (3). After monotherapy with pasireotide, cabergoline and ketoconazole were sequentially added in those patients without biochemical control. Thereby, a total of 29%, 53%, and 88% of patients, respectively, normalized UFC.

Therefore, several studies by now have demonstrated that pasireotide is able to provide clinical benefit in patients with Cushing's disease, by reducing hypercortisolism and improving associated signs/symptoms. Due to the potential for increases in glucose levels, studies focusing on the optimal management of hyperglycemia during treatment with pasireotide are needed. Pasireotide may represent a specific treatment for corticotrophic adenomas.

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Stephan Petersenn is a speaker for and on advisory committees for Novartis and Ipsen, and is a speaker for Pfizer.

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

PITUITARY TUMORS: CHALLENGES

Chair: Kalmon Kovacs – has no relationships to disclose.

PITUITARY TUMOR SURGERY: CHALLENGES TO INVASIVE LARGE ADENOMAS

Shozo Yamada

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Recent advances in surgical technology including endoscopy, neuronavigation have led to significant evolution of the current transsphenoidal surgery and have allowed neurosurgeons to improve the surgical results of pituitary adenomas with lower complications. However, safety radical removal of extremely large and/or invasive adenomas remains a big challenge for even experienced pituitary surgeons. Moreover, incomplete tumor resection by conventional transsphenoidal surgery in such tumors is often associated with critical bleeding in residual adenoma. Not only the size but rather the configuration of adenoma restrict the degree of resection. Large adenomas with hourglass constriction, lobulations, and asymmetric extension are usually considered contraindication of transsphenoidal surgery. Most of these adenomas have been traditionally treated with transcranial approach with or without following postoperative radiotherapy. However, the transcranial approaches have undoubtedly higher risk of morbidity compared to transsphenoidal approach. Therefore, following surgical approaches have been adopted in our center to avoid the inherent risk of fatal perioperative complications; extended transsphenoidal approach for the relatively-small adenomas or simultaneous combined supra- and infrasellar approach, i.e. combined transcranial and transsphenoidal approach, for the invasive giant adenomas. The former approach has been performed in 9 patients and the latter has been in 29 patients with higher radical removal rates (8/9, 25/29). There have been no critical complications including postoperative hemorrhage or infarction. Since most of these unusual adenomas invasively perforate the sellar diaphragm and lack a sort of well-defined tumor capsule, wider operative view obtained by extended transsphenoidal approach or simultaneous manipulation from both below (transsphenoidal approach) and above (transcranial approach) of tumor under direct vision was more effective and safer for the removal of extremely large and/or invasive adenomas.

Shozo Yamada has no relationships to disclose.

TOWARD A MEANINGFUL DEFINITION OF PITUITARY CARCINOMA

Bernd W. Scheithauer

Mayo Clinic

Criteria for a relevant diagnosis of pituitary carcinoma are sorely needed. Historically and at present, the designation has required documentation of metastatic adenohypophysial tumor. When present, survivals are in many instances short. During past years, it has become apparent that a) only a minority of pituitary carcinomas arise de novo, most having had their basis in multiply recurrent adenomas showing progressive transformation, and b) that histologic grade of the primary and secondary tumor may be a factor in predicting behavior. Not all adenohypophysial cells or hormonal adenoma subtypes are equally prone to malignant transformation. Most pituitary carcinomas are ACTH- or PRL-producing; nonfunctioning carcinomas are very uncommon. Biomarkers related to or facilitating the assessment of tumor aggressiveness include mitotic indices, MIB-1 labeling indices and other immuno-markers, including p53, p21, topoisomerase-2 alpha, hypoxia inducible factor, matrix metalloproteinase, microvascular density, and the expression of fibroblast growth factor and its receptor as well as of vascular endothelial growth factor. Correlation of these markers with aggressiveness is rather poor. This is in part due to the fact that such a basic operative and radiographic feature as invasion is key to recurrence and metastasis. Lastly, conventional chemo- and radiation therapy are palliative at best. Preliminary studies of MGMT immunoreactivity and of MGMT promoter methylation suggest they will play an important role in the treatment of this rare disease.

Bernd W. Scheithauer has no relationships to disclose.

PITUITARY TUMOR PATHOGENESIS

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Although pituitary adenomas have been shown to be monoclonal proliferations, the exact pathogenesis of these tumors remains uncertain. The role of hypothalamic hormones in the pathogenesis of pituitary adenomas has been shown in animal models and some studies suggest that hypothalamic hormones may have a role in the pathogenesis of human pituitary tumors (1). Gain of function of certain genes including GNAS, PKA, RAS, PTTG, FGF/FGFRs have been associated with pituitary tumor development. Loss of function of specific genes includes MENIN, RB1, p27, p18, p16, GADD45 gamma and MEG3a have been associated with various types of adenomas. More recent studies with gene expression profiling have identified several candidate genes that may be important for pituitary adenoma pathogenesis. These include Pit-1 and GAG1 in prolactinomas and loss of genes in the 11p region of aggressive prolactinomas. Other studies have shown roles for LGALS3, hASH1, ID2 and TLE-4 genes in pituitary carcinoma development. Studies of the role of microRNA in pituitary tumor development have implicated specific miRs such as miR-15 and miR-16-1 in some pituitary tumors. One study of ACTH adenomas and carcinomas implicated miR-493 and miR-122 over expression in pituitary tumor progression.

An emerging area of research that may help to elucidate the pathogenesis of pituitary tumors includes studies of tumor stem-cells(2,3). The folliculo-stellate cell has been implicated as a possible side population cell in non-neoplastic pituitaries. More recent reports on the isolation and characterization of pituitary adenoma stem-like cells have shown that these cells are tumor-initiating cells using serial transplantation animal experiments.

The pathogenesis of human pituitary tumors most likely includes a combination of several of these mechanisms.

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None of the authors have any relationships to disclose.

CHALLENGES IN PITUITARY TUMOR THERAPY

Luis V Syro, MD

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Patients with aggressive pituitary adenomas are clinically difficult to manage. Repeat surgeries, pharmacologic treatment and radiotherapy are employed, often in combination, yet many patients experience tumor regrowth. Pituitary carcinomas present particular diagnostic and therapeutic challenges due to craniospinal and/or systemic metastases. In 2004, Fadul et al first reported the successful use of temozolomide (TMZ) in pituitary carcinomas. In 2006, TMZ was administered to a 42-year-old man with an aggressive PRL-producing adenoma. Temozolomide is an alkylating chemotherapeutic agent related to a series of imidazotetrazines. Response to TMZ therapy is related to expression levels of O-6-methylguanine-DNA methyltransferase (MGMT), a DNA repair enzyme. To date, according to literature, 43 patients (28 with adenomas and 15 with pituitary carcinomas) have been treated with temozolomide. In carcinomas 10 out of 15 responded (66%) and in adenomas 16 out of 28 responded (57%). 4 out 28 were stable (14%). With respect to MGMT immunoreexpression, there is presently no consensus regarding quantification or "grading" of reactivity. Thus, it is difficult to draw firm conclusions regarding levels of MGMT expression and response to treatment. Nevertheless, to have high MGMT immunoreexpression seems to be more predictive for no response to TMZ than low or absent MGMT.

We feel strongly that determination of MGMT immunoreactivity is of clinical value and that assessment of MGMT immunoreactivity as well MGMT promoter methylation status should be pursued. In patients who do not respond to TMZ another option is possible. More research should be performed to clarify which patients would benefit from Bevacizumab, an anti-VEGF monoclonal antibody. We do hope that targeted therapy directed to specific molecular alterations will be available for pituitary neoplasms in the near future.

Luis V Syro, MD has no relationships to disclose.

PITUITARY HORMONE ASSAYS

Chair: Lawrence Frohman – has no relationships to disclose.

IS THE GH ASSAY VALID?

Christian J. Strasburger

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The validity of growth hormone assays is of paramount importance not only in the court-proof identification of athletes abusing GH as a performance enhancing drug, but also for clinical endocrine disorders. GH level determinations by immunoassay represent a cornerstone both in the diagnosis and follow-up of acromegaly and in GH deficiency. In both settings GH determinations are performed in the context of dynamic testing such as OGTT in acromegaly and stimulation tests for GHD. Owing to the vast discrepancy between the results of different commercially available GH assays, cut-off recommendation for stimulation tests in the diagnosis of GHD or for the diagnosis of acromegaly in OGTT must be assay-specific and cannot be generalised from one method to the other. A recent interdisciplinary consensus statement (Clinical Chemistry 57:4, 555-559 (2011)) recommends the use of the international reference preparation 98/574 hGH for calibration and the use of assays specific for the 22 kDa form of human GH. A lower detection limit of 0,05 mg/l or better is recommended. Each assay method should specify the degree of interference by the circulating extracellular domain of the GH receptor (GHR) as well as the antibody specificity and their cross-reactivity with related hormones such as placental lactogen and placental GH. The use of conversion factors between different assays is strongly discouraged because the conversion factors do not account for all assay differences.

For the measurement of growth hormone levels in the presence of the GH receptor antagonist Pegvisomant, the majority of GH assays are not suitable. Both an overestimation and underestimation of the true endogenous GH level may occur if both or one of the antibodies employed cross-react with the receptor antagonist usually circulating in blood at a concentration approximately 1000-fold higher than hGH. A falsely low result may be obtained when the immobilised antibody does cross-react with Pegvisomant, therefore binding the drug proportional to its abundance in serum, and if further the labelled antibody does not cross-react with Pegvisomant. The measurement of GH levels in the presence of Pegvisomant require the use of antibodies devoid of any cross-reaction with the GH receptor antagonist, which has a very similar structure to wild type growth hormone.

Endocrinologists should care and know about the specifications of the GH assay used for the determination of GH levels in their patients' sera.

Christian J. Strasburger has no relationships to disclose.

USE OF IGF-I MEASUREMENTS TO MONITOR DISORDERS OF GROWTH HORMONE SECRETION

David R. Clemmons, MD

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Insulin-like growth factor-I (IGF-I) is a growth hormone dependent peptide. Although its concentrations are unequivocally elevated in acromegaly and suppressed in the significant percentage of patients with growth hormone deficiency, wide variations in IGF-I concentrations within the normal population make it difficult at times to discriminate between normal and abnormal values. Because of this difficulty the assay requirements for measurement of IGF-I need to be quite stringent. The most important requirement for a reference laboratory IGF-I assay is an adequate number of normative subjects that span all age ranges to be analyzed. IGF-I concentrations vary significantly during childhood development reaching a peak concentration at puberty and then decline. However even in adulthood the difference between the mean concentration for 20 year olds is twice as great as that for 60 year olds. Therefore an adequate number of normative subjects in each decade of adult life is required in order to correctly diagnose GH deficiency or excess. An additional difficulty in measuring IGF-I is the presence of IGF binding proteins. Unlike insulin and most other peptide hormones, IGF-I circulates in a bound form and less than 1% of the total IGF-I in serum is free. Because binding proteins can interfere with each type of IGF-I measurement a method must be utilized that adequately eliminates binding protein interference. Additional requirements for reference laboratories include utilization of a universally accepted standard that is commutable among various laboratories, adequate characterization of the antibody or antibodies utilized to determine that they have adequate sensitivity and specificity, proof that recovery of the pure standard is adequate in clinical conditions with binding protein excess and adequate reproducibility of results such that the interassay variability is less than 15%. Assays meeting these requirements would generally be useful for confirming the diagnosis of acromegaly and are often helpful in assessing the degree of growth hormone deficiency. Even the most rigorously performed and reproducible assay however has limitations. Acromegaly is quite a rare disease and high IGF-I concentrations are by definition present in 2.5% of the normal population. Therefore an IGF-I measurement should always be accompanied by a growth hormone suppression test to correctly diagnose acromegaly. However when the diagnosis is established measurement of IGF-I is quite useful in monitoring the response to treatment. The major problem in assessing hypopituitarism is the presence of confounding factors which can elevate the IGF-I such as obesity, however IGF-I is quite useful in monitoring the response to growth hormone administration in order to avoid toxicity. In summary IGF-I measurements are useful when performed in a high quality, reproducible assay. Future improvements in methodology such as the use of mass spectroscopy should further enhance assay reliability.

David R. Clemmons, MD is a consultant for Pfizer, Novartis, Ipsen, and Lilly.

SALIVARY CORTISOL ASSAYS

Hershel Raff, PhD

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Measurement of salivary cortisol has emerged as an indispensable tool for the evaluation of disorders of the HPA axis in humans. Measurement of an increased unstressed nighttime salivary cortisol is an important first step to screen patients for endogenous Cushing's syndrome. Furthermore, measurement of salivary cortisol in response to cosyntropin can be useful in the diagnosis of adrenal insufficiency, particularly in patients with difficult venous access or changes in plasma binding proteins. Salivary cortisol can be measured by direct immunoassays (including RIA, FPIA, ECLIA, and ELISA) as well as liquid chromatography-tandem mass spectrometry (LC-TMS). They all provide excellent sensitivity for Cushing's syndrome (92-100%). LC-TMS may have an advantage in specificity (91%), although the specificity of immunoassays is also quite good (77-100%). The major caveats for salivary cortisol measurements are preanalytical errors such as non-compliance with the timing of the home sampling and contamination of the saliva sample (usually with hydrocortisone [authentic cortisol] handcreams and ointments). Finally, in addition to its importance as an initial diagnostic tool, salivary cortisol is also very useful to follow patients after transphenoidal pituitary surgery for Cushing's disease; a post-operative increase in nighttime salivary cortisol strongly suggests a treatment failure or recurrence after an initial cure. Measurement of salivary cortisol is now available at all major reference laboratories and provides a simple and highly accurate screening test for Cushing's syndrome. Nighttime salivary cortisol sampling should be obtained on any patient in whom there is a tangible index of suspicion for endogenous hypercortisolism.

Hershel Raff, PhD has no relationships to disclose.

ABSTRACTS
HOT TOPICS

EARLY MEDICAL TREATMENT OF PITUITARY LESIONS, THE JOHNS HOPKINS EXPERIENCE 1896 TO 1912

Courtney Pendleton, B.S., Nestoras Mathioudakis, M.D., Alfredo Quinones-Hinojosa, M.D.

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Introduction: At the turn of the twentieth century, the pituitary body remained an enigma; a plethora of surgical and medical approaches to treatment of disorders of the pituitary were attempted, with varying success.

Methods: Following IRB approval, and through the courtesy of the Alan Mason Chesney Archives, we reviewed the Johns Hopkins Hospital surgical files from 1896-1912; approximately 26,000 surgical interventions were reviewed. All neurosurgical cases performed by Harvey Cushing, and a selection of non-neurosurgical cases performed by Cushing, were further analyzed. We recovered thirty-seven patients who Cushing treated with surgical intervention directed at the pituitary gland. Although we have previously reported the surgical interventions Cushing employed in these cases, his use of medical treatments to complement operative treatment for disorders of the pituitary body remains unexplored.

Results: In total, 37 patients underwent surgical intervention for suspected sellar lesions. Of these patients, 9 presented with symptoms of acromegaly, 1 presented with symptoms of gigantism, and the remaining 27 presented with various symptoms of hypopituitarism.

Cushing treated 19 patients with pituitary extract during their inpatient admissions; 5 of these patients were diagnosed with acromegaly prior to treatment with pituitary extract. The extract used varied in concentration from 0.1 to 1 grams in injectable solutions, and 3 to 12 'grains' three times daily in preparations taken by mouth. Anterior pituitary extract was administered in fifteen patients; posterior pituitary extract was administered in five patients, whole gland extract was administered to four patients, and four patients received unspecified extracts. Five patients received pituitary extracts from more than one source. Pituitary extract was obtained from a commercial source (Armour).

There were 20 admissions where patients were given pituitary extract; the mean length of stay for these admissions was 41.8 days. There were 24 admissions where patients did not receive pituitary extracts; the mean length of stay for these admissions was 38.8 days.

Immediate post-operative outcomes and long-term outcomes for patients with follow-up data did not correlate with the administration of pituitary extract during the inpatient stay.

Conclusions: The data uncovered in this historical review demonstrates that Cushing employed medical treatment for a wide variety of sellar pathology. As Cushing developed his operative approach to the pituitary gland, his use of pituitary extract decreased. The role of the pituitary gland in disease states was still under investigation at the turn of the twentieth century, which led to misdirected medical treatment, such as the administration of pituitary extract to patients with acromegaly.

None of the authors have any relationships to disclose.

ABLATION OF POMC NEURONS INDUCES AN OBESE PHENOTYPE CHARACTERIZED BY DECREASED FOOD INTAKE AND ENHANCED ANXIETY IN UNSTRESSED MICE

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POMC neurons in the arcuate nucleus of the hypothalamus are central components of systems regulating stress response and appetite. We have generated a transgenic mouse model in which the RNase III ribonuclease Dicer has been specifically deleted from POMC expressing neurons using a cre-lox system, leading to depletion of mature microRNAs and cell death. Mice are born phenotypically normal and at the expected genetic ratio. On PND1, hypothalamic POMC-mRNA expression was unchanged in Dicer-KO mice but at six weeks it was reduced by 96% from the levels in WT animals ($p=0.0009$) and no POMC neurons could be detected in the arcuate nucleus by immunostaining. Weight gain was significantly more prominent in Dicer-KO mice: 5 months old Dicer $-/-$ and $+/+$ males weighted 52.7 ± 7.3 and 36.2 ± 3.2 g respectively ($p < 0.01$). Surprisingly, food intake was significantly lower in Dicer-KO mice (0.23 ± 0.05 g/body weight^{0.75} vs 0.34 ± 0.06 in WT, $p < 0.05$). Physical activity was similar in all genotypes, but Dicer $-/-$ had decreased energy expenditure (dark-phase heat production 12.6 ± 2.1 kcal/h/kg vs 16.0 ± 1.75 in WT, $p < 0.05$) which could not be attributed to thyroid dysfunction as free thyroxin levels were similar among groups. AgRP, Leptin receptor and NPY mRNA levels were reduced by 87% ($p=0.003$), 32% ($p = 0.02$), and 26% ($p=0.09$) respectively, potentially explaining the decreased food intake in these mice. POMC and CRFR1 mRNA levels were undetectable in the anterior pituitary gland of Dicer-KO mice, consequently basal and stress-induced corticosterone levels were undetectable in these mice. Despite this lack of activation of the classical stress response, Dicer-KO mice exhibited an anxiogenic phenotype as assessed by the dark-light transfer test, the elevated plus maze and the acoustic startle response. In conclusion, ablation of POMC neurons leads to enhanced anxiety and the development of obesity despite decreased food intake and glucocorticoid deficiency.

None of the authors have any relationships to disclose.

HYPOPITUITARISM IN RETIRED PROFESSIONAL FOOTBALL PLAYERS: A PROSPECTIVE STUDY

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Introduction: Hypopituitarism is a known sequelae of moderate/severe traumatic brain injury (TBI). Less is known about the relationship of contact sports and recurrent concussion on pituitary function. Herein we describe initial study results addressing the relationship between concussion, subsequent hormonal function and quality of life (QOL) in retired football players.

Methods: From a database of approximately 2800 retired National Football League players, subjects were identified who meet the following criteria: age 30-65 years, 2 or more years in NFL, poor QOL (SF-36 Mental Component Score score<49). Eligible subjects underwent repeat SF-36 survey, sexual function survey (International Index of Erectile Function; ED criteria IIEF<25), metabolic syndrome and pituitary testing: cortrosyn and glucagon stimulation, IGF-1, LH/FSH, testosterone, T4/TSH, prolactin; (GH deficiency: peak GH<3ng/ml; hypogonadism: total testosterone <265ng/ml). Subjects with/without hormonal deficiency (HD vs non-HD) were compared.

Results: Between 3/2009-1/2011, 72 subjects completed testing. At least one HD was documented in 29 (40%) subjects: 27(37.5%) with GHD and 6(8%) with hypogonadism. Comparing HD vs non-HD subjects, age (47±8 vs 47±11 year), median number seasons played (4 vs 5) and median number concussions (4, range 0-50 vs 5, range 0-45) were similar. Compared to non-HD subjects, HD subjects had lower SF-36 MCS scores (33±10 vs 38±10, p=0.02), higher BMI (35.2±6.4 vs 31.9±5.1, p=0.03) and higher rates of metabolic syndrome: 18/29(62%) vs 19/43(44%) (p=0.11 Fisher's exact). Erectile dysfunction was reported in 14% of both groups.

Conclusion: In this cohort of retired professional football players with known poor QOL, hypopituitarism was observed in 40% including 37% with GHD and 8% with hypogonadism. HD subjects were more likely to have worse QOL, higher BMI and a trend toward higher rates of metabolic syndrome. Risk factors for HD remain unclear but possible inconsistencies in concussion reporting may be a confounder. Neurobehavioral outcomes and GH replacement trial are in progress.

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Ronald Swerdloff receives consulting fees from Lilly.

ABSTRACT
POSTER PRESENTATIONS

A CASE OF AN HYPOTHALAMIC INFLAMMATORY LESION SUCCESSFULLY TREATED WITH IMMUNOSUPPRESSIVE THERAPY

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Pituitary autoimmune inflammatory processes are the most common among the chronic inflammations that primarily affect the pituitary gland. Autoimmune hypophysitis can involve the anterior pituitary or the infundibular stem and the posterior lobe or both of them. Few data are available about the hypothalamic involvement in autoimmune disease.

We report the case of a 48 year old woman that developed in February 2010 acute onset of polyuria, polydipsia, asthenia with diarrhea and vomiting. She underwent a brain MRI that showed a 13 mm suprasellar lesion isointense in T1, hyperintense in T2 FLAIR with homogeneous enhancement. Hormonal testing showed panhypopituitarism and hyperprolactinemia, so the patient was started on replacement therapy with hydrocortisone, levothyroxine and desmopressin. Visual field was normal and we decided for a new MRI imaging in April 2010 that showed a mild increase of the lesion (14 mm). The patient underwent biopsy of the lesion via transphenoidal approach ("diffuse infiltration of lymphocytes, CD20+ and CD3+, plasma cells and macrophages. No B clonality"). Dosing of anti-pituitary antibodies came positive, while anti-hypothalamus were negative. In May 2010 treatment with prednisone was started. In November 2010 the patient underwent a new visual field evaluation with evidence of bitemporal hemianopsia and a new MRI that was unchanged. Therefore treatment with azathioprine and iv dexamethasone, then replaced with oral prednisone, was started, with steroid induced diabetes mellitus later onset that required insulin therapy. A new MRI in January 2011 showed a striking reduction of the hypothalamic lesion. Visual field evaluation showed mild improvement of the deficit. Hormonal testing confirmed panhypopituitarism. New dosing of anti-pituitary antibodies came negative.

In conclusion, in the differential diagnosis of purely hypothalamic lesions, an autoimmune inflammatory etiology should be considered. Although steroid treatment is advisable as first line therapy, it can prove unsuccessful requiring association with immunosuppressive agents.

None of the authors have any relationships to disclose.

Poster #2

A CASE OF SYNCHRONOUS ACTH AND PROLACTIN SECRETING PITUITARY ADENOMAS

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Double pituitary adenomas are defined as two histologically and ultrastructurally distinct tumours occurring simultaneously in the pituitary. They represent up to 2.6% of pituitary adenomas in surgical series. Up to 3.3% of patients with Cushing's disease have been found to have double or multiple pituitary adenomas.

We report the case of a 58 years old male patient whose medical history began in 2002 with erectile dysfunction; hormonal testing showed hyperprolactinemia (98 ng/ml) with low levels of gonadotropins; an MRI showed a 6 mm area in the lateral portion of the right pituitary lobe. Treatment with cabergoline was started with normalization of prolactin levels. The following MRI in 2005 and 2008 showed shrinkage of the pituitary lesion. In 2005 the patient began to manifest weight gain, hypertension and diffuse skin redness. In January 2010 the patient came to our attention and underwent dosing of midnight cortisol (193 ng/ml), cortisol after dexamethasone 1 mg overnight (174 ng/ml), cortisol after high dose dexamethasone (27 ng/ml), ACTH (54 pg/ml) and CRH testing with positive response of ACTH and cortisol, suggestive for Cushing's disease. A new MRI was negative. In April 2010 the patient underwent bilateral inferior petrosal sinus sampling that showed significant pituitary-to-peripheral ratio and, in May 2010, he underwent pituitary exploratory surgery with evidence of a dyshomogeneous area localized in the right pituitary lobe corresponding to the known lesion that shrank during cabergoline treatment and a millimetric white-coloured midline area suspicious for pituitary adenoma that was surgically removed. Post-operatively the patient's clinical conditions improved with evidence of secondary hypoadrenalism suggesting Cushing's disease remission. The histological examination confirmed a pituitary adenoma with positive immunostaining for ACTH and negative for prolactin.

We report the case of an ACTH producing microadenoma synchronous to a prolactin secreting microadenoma, although not confirmed histologically, shrank by medical treatment.

None of the authors have relationship to disclose.

Poster #3

A META-ANALYSIS OF THE EFFECTS OF OCTREOTIDE ON TUMOR MASS IN ACROMEGALY

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Over the recent years, there has been growing evidence that somatostatin analogs (SSAs) are able to induce tumor shrinkage in patients with acromegaly, but the clinical relevance of this effect is still unclear since the information on this issue mostly derive from studies which are limited in terms of number of patients and heterogeneous for length and type of follow-up and for different SSAs used. In this study, we performed a meta-analysis to assess the size of tumor shrinkage induced by octreotide in patients with acromegaly. Primary endpoints were proportion of responders and the mean percent reduction in tumor volume. Exact method for calculating confidence intervals for individual and pooled proportion of response were used. The electronic searches revealed 1547 articles. Out of these, 1348 were discarded because not meeting the eligibility criteria. The text of the remaining 125 was fully examined and after revision, 42 studies fulfilling eligibility criteria were selected for data extraction and analysis. 2421 patients were included in the analysis ranging from 6 to 189 per trial. Octreotide was shown to induce shrinkage in 52% [95% C.I.: 49%-54%] of treated patients with the prevalence being higher when the tumor dimensions were reported as volume, with a proportion of responders of 59%, [95% C.I.: 56%-62%]; in patients treated with octreotide LAR the proportion increased to 70%, [95% C.I.: 67%-74%]; in patients receiving octreotide as first-line therapy it was 63%, [95% C.I.: 60%-66%] and in those achieving safe GH values 72%, [95% C.I.: 64%-79%]. Analyzing the few studies in which the entity of shrinkage was defined, the weighted mean percent reduction in tumor size was 29.3% [95% C.I.: 16.8%-46.2%], with greater effects in patients treated with octreotide LAR: 49.5% [95% C.I.: 29.1%-69.8%]. This meta-analysis showed that octreotide LAR may induce tumor shrinkage in up to two-third of patients with acromegaly.

M. Spinello is a Novartis employee.

A. Giustina receives consulting and lecture fees from Ipsen.

The other authors have no relationships to disclose.

Poster #4

A PATIENT WITH NELSON SYNDROME SHOWED IMPROVEMENT WITH CABERGOLINE THERAPY

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Cushing's disease still represents a challenge nowadays, transsphenoidal surgery is not always curative, and options are drug therapy and adrenalectomy for the control of the disease.

Case Report: A 27 years-old woman with Cushing's disease still presented a severe clinical picture after two transsphenoidal surgeries in 2003. Remission was not expected due to right cavernous sinus invasion observed on Magnetic Resonance image (MRI). She was submitted to radiotherapy in 2004 due to the refractoriness and severity of the disease. As she did not have relevant improvement with ketoconazole 1200 mg/day, she was submitted to total bilateral adrenalectomy (TBA) in October 2009 and is under prednisone and fludrocortisone replacement since then. ACTH level increased from 158 pg/ml before surgery to 354 pg/ml and 534 pg/ml, 3 and 5 months after transsphenoidal surgery, respectively. At that moment, cabergoline was initiated at a dosage of 1.5 mg /week. A CTH level was 112 pg/ml, 61 pg/ml and 188 pg/ml after 2, 6 and 12 months after cabergoline therapy was started, respectively. Tumor did not enlarged after TBA.

Discussion: Cabergoline could be a good option for the control of refractory Nelson's Syndrome.

None of the authors have any relationships to disclose.

This abstract includes discussion of products unlabeled for use as approved by the FDA / equivalent regulatory authority in the country in which the study/trials were performed.

ACROMEGALY AND PREGNANCY

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Introduction: Acromegaly affects childbearing age women. However the coexistence of pregnancy is a rare event. Concerning materno-fetal complications, the manner how acromegaly and its treatment affect pregnancy is still a matter of debate. Materials and methods: retrospective analysis of our patients followed from 1990 to 2010. Results: seven patients became pregnant. All patients had active acromegaly due to expansive/invasive macroadenoma and pregnancy occurred spontaneously (table)

mother													newborn		
pre-conception			Pregnancy				labor delivery	Postpartum							
n	Age	treatment	Treatment	GH	IGF-I	complications /outcome	(we)	GH	IGF-I	Breast feeding	weight (Kg)	Height (cm)	abnormalities		
1	31	S	none	↑	↑	none	39	↑	↑	declined	3850	49	no		
2	25	S	none	↑	↑	none	39	↑	↑	10	3250	51	no		
2	26	S	none	↑	↑	none	39	↑	↑	5	3650	51	no		
3	34	S(2)+RT+SA	SA first 5		normal	none	39	↑	↑	6	3750	50	no		
4	38	none	none	↑	↑	gestational diabetes/ headache	38	↑	↑	8	3300	50	uretral stenosis		
5	30	S(2)+AS	SA first 4 mo	normal	normal	diabetes improvment	37	↑	↑	5	3500	50	no		
6	34	S+SA	SA first 4 we	normal	normal	none	39	↑	↑	1	2150	44	uretral stenosis		
7	39	S+SA	SA first 4 we	↑	↑	miscarriage	NA	↑	↑	NA	NA	NA	NA		

S= Surgery RT= Radiotherapy SA= Somatostatin analogues mo=months we=weeks NA= not applicable

Comments: Pregnancy evolved without complications in our patients, except the one not previously operated on. Hormonal levels normalization was observed in some patients, confirming previous reports. Concerning the cause of the urinary tract alterations of two newborns no conclusion can be inferred: no SA was used in one case and, the other, small for gestational age, was an offspring of a mother with diabetic complications.

*Marcello Bronstein is a speaker for Novartis Oncology.
The other authors do not have any relationships to disclose.*

Poster #6

ACUTE EVALUATION OF PITUITARY FUNCTIONS IN PATIENTS WITH CRIMEAN-CONGO HEMORRHAGIC FEVER

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Context: Crimean Congo Hemorrhagic Fever (CCHF) can cause a fatal hemorrhagic syndrome. Pituitary ischemia/infarction and necrosis are known causes of hypopituitarism, often remaining unrecognized due to subtle clinical manifestations.

Objective: Our aim was to evaluate whether CCHF can affect pituitary functions.

Subject and methods: Levels of serum free T3, free T4, TSH, GH, IGF-I, prolactin, cortisol, testosterone (in males) and estrogen (in females) were studied in 20 patients who had been diagnosed with CCHF. TRH, LH-RH and 1 μ g adrenocorticotropin tests were conducted in all patients. Serum levels of basal and after stimulation tests of cortisol, FSH, LH, prolactin, and TSH were measured. Hypothalamo-pituitary region was examined by magnetic resonance imaging in two patients diagnosed with hypocortisolism. Their mean \pm standard deviation (SD) was calculated. This study was approved by the local ethics committee.

Results: We found cortisol insufficiency in 2 (10%) of the 20 patients diagnosed with CCHF. However, hypophyseal magnetic resonance imaging findings were normal in these 2 patients. None of the patients had GH, TSH, FSH-LH deficiencies.

Conclusion: To our knowledge, this is the first study in the literature which investigates the role of CCHF on pituitary functions. We found that cortisol insufficiency may occur in patients diagnosed with CCHF; however, studies on larger patient populations are required to make definite conclusion on this issue.

Key words: Crimean-Congo hemorrhagic fever, hypopituitarism, stimulation tests.

None of the authors have any relationships to disclose.

Poster #7

ADULT PATIENT WITH NEUROFIBROMATOSIS TYPE 1 WITH DOUBLE PITUITARY AND CONSERVED FUNCTION

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A 28-yr-old female patient with mild neurofibromatosis type 1 (axillary freckling, skin café-au-lait spots, Lisch nodules, no manifest neurofibromas) underwent an encephalic MRI showing a duplication of both pituitary gland and stalk. No evidence of optic nerve gliomas or midline malformations were found, except a 6 mm diencephalic mass with signal similar to brain stem. The patient had no previous signs or symptoms of pituitary dysfunction. In particular, she had normal facies and habitus, normal menses, no asthenia. Blood analyses showed normal pituitary function. A Three-Tesla encephalic MRI further revealed a mild asymmetry between the two pituitary glands. Moreover, the diencephalic mass was attributed to incomplete hypothalamus duplication, hypothalamus enlargement being present in a half of patients with duplication of the pituitary gland. Recently, the woman had a spontaneous pregnancy and was delivered of a healthy newborn. She experienced only a peripartum transient gestational diabetes insipidus which was treated with desmopressin and completely resolved after delivery that was carried out by elective caesarean section. After three months from lactation discontinuation, normality of anterior pituitary function, assessed by baseline hormonal levels and dynamic testing, was confirmed. A MR angiography, carried out to assess basilar artery abnormalities shown by 3T MRI, revealed a partial basilar artery duplication, a rare malformation that has been reported in pituitary duplication associated with complicated midline and skull base severe anomalies. Up to now, pituitary duplication has been described in newborn, children or adolescents with additional neural/craniofacial anomalies, oropharyngeal masses or vertebral malformations, frequently associated with precocious or delayed puberty. To our knowledge this is the first report of pituitary duplication without other abnormalities in an adult subject with a genetic disorder (neurofibromatosis type 1) not associated with organ duplication. The inductive mechanism resulting in pituitary duplication remains unknown.

None of the authors have any relationships to disclose.

Poster #8

BASELINE MRI FINDINGS AS PREDICTORS OF HYPOPITUITARISM IN PATIENTS WITH NON-FUNCTIONING PITUITARY ADENOMAS

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Background: The magnitude of pituitary hypofunction in patients with non-functioning pituitary adenomas (NFPA) is variable even in patients with similar size tumors base on classical linear measurement.

Objective: To determine if any feature on pituitary MRI, other than linear size, is predictive of hypopituitarism in patients with NFPA.

Methods: We performed a retrospective descriptive analysis based on evaluation of the initial MRI studies and the assessment of the pituitary hormone functional status at baseline of 54 consecutive patients with NFPA from the McGill University Health Centre neuroendocrine clinic (Montreal, Canada).

Results: Fifty-four subjects were included [55% males, 3 micro and 51 macroadenomas]. Twenty-three had at least one critical pituitary hormone deficiency (CPHD), which includes central hypoadrenalism and/or hypothyroidism. At baseline clinical/biochemical hormonal evaluation, 40 subjects had at least one pituitary hormone deficiency while seventeen had deficiency of > 3 hormones.

Tumours that showed no enhancement after gadolinium infusion on baseline MRI were less likely to be associated with CPHD (Sensitivity of 85.7%, Specificity 47.7%, NPV 95.5%, PLR 1.64). No patient without stalk deviation had CPHD (sensitivity 100%, specificity 47.9%, PLR 1.92). Tumors without CS invasion were less likely to have CPHD (sensitivity 85.7%, specificity 46.8%, PLR 1.61). Tumors with linear volume of < 3cc were less likely to have CPHD (Specificity 88.5%, sensitivity 41.9%, PPV 81.2%, PLR 3.634). Three or more hormonal deficiencies were less frequently seen in patients which tumors on MRI showed no enhancement after gadolinium, no stalk deviation and no cavernous sinus invasion. None of the patients with microadenomas had CPHD.

Conclusion: In patients with NFPA, baseline pituitary MRI features of non-enhancement, absence of pituitary stalk deviation and cavernous sinus invasion appear to be favorable for the absence of CPHD and of 3 or more pituitary hormonal deficits. Studies with larger number of subjects might be needed to confirm our findings.

None of the authors have any relationships to disclose.

Poster #9

BASELINE MRI FINDINGS AS PREDICTORS TUMOR GROWTH IN PATIENTS WITH NON-FUNCTIONING PITUITARY ADENOMAS

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Background: In non-functioning pituitary adenomas (NFPA), probability of growth varies from 10 to 70%. Yet the decision to intervene surgically often depends on such probability. Improving our ability to predict tumour growth may have significant clinical implications.

Objective: To determine if any radiological features on pituitary MRI is predictive of tumor growth in patients with NFPA.

Methods: We performed a retrospective descriptive analysis based on chart review and evaluation of the initial and follow-up MRI studies of consecutive patients with NFPA from the McGill University Health Centre neuroendocrine clinic (Montreal, Canada). We included only patients with at least 2 MRI tests, at least 3 months apart, prior to any surgical or medical intervention.

Results: Twenty-eight subjects were included in the study [47% males, 3 micro and 25 macroadenomas]. The mean interval between baseline and last follow-up MRI was 31 months (range 3–70). During the follow up period, the adenomas in 12 patients (43%) showed ≥ 20% tumor growth, while 17 (61%) exhibited at least 10% tumor growth. Tumours with isointensity on T2-weighted images were significantly less likely to show growth of 20% or more in subsequent MRI [p=0.029, 95% CI=1.198-31.16, OR=6.11; PPV (for no growth) 79%]. Tumours that appeared heterogeneous were more likely to grow by at least 10% [p=0.045, 95% CI= 1.039-28.53, OR=5.44; Sensitivity: 82.4%, specificity 63.6%, PPV 78%]. However, this variable showed no correlation with growth of more than 20%. In our series, tumours that did not enhance after gadolinium injection were significantly more likely to grow by > 20% [p=0.019, sensitivity 36%, specificity 67%].

Conclusion: At baseline pituitary MRI, features of isointensity on T2-weighted images, heterogeneity and enhancement can help determining the potential of tumor growth in NFPA. In this study, linear size, estimated tumor volumes, intensity on T1-weighted images, cystic appearance, invasiveness or stalk deviation at presentation were all non predictors of tumor growth in NFPA.

None of the authors have any relationships to disclose.

Poster #10

CABERGOLINE AND VALVULAR HEART DISEASE: A TRANSVERSAL STUDY

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Background: Ergot-derived dopamine receptor agonists, mainly cabergoline, are the treatment of choice for prolactinomas. High doses of cabergoline have been associated with valvular heart disease in patients treated for Parkinson's disease. However, the impact of the conventional dosage for patients with prolactinomas is still controversial.

Objectives: To evaluate the prevalence of valvular heart disease in patients with prolactinoma in our institution.

Patients and Methods: This transversal study included echocardiographic evaluation in 44 patients on cabergoline from our clinic: 27 with macroprolactinoma (17 women and 10 men – mean age 35.5 years) and 17 women (mean age 40.5 years) with microprolactinoma.

Results: Time of use of cabergoline was 31 ± 19 months with a mean cumulative dose of 294 ± 369 mg (mean \pm SD). The median dose was 2.0 mg per week. 66% of patients showed mild mitral and/or tricuspid regurgitation without clinical impact. This effect was not dose-dependent (P=0.66).

Conclusion: Due to the study design the high prevalence of valvular heart disease, as compared with populational studies, cannot be certainly attributed to cabergoline therapy, but the echocardiographic surveillance should be warranted.

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None of the authors have any relationships to disclose.

Poster #11

CHALLENGES OF THE GH/IGF-1 AXIS INTERPRETATION

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Background: Many patients with acromegaly are diagnosed at earlier stages of disease and milder biochemical abnormalities. At the same time, as IGF-1 testing is increasingly performed, we have a growing number of patients with mild elevation of IGF-1. In these situations the results of oral glucose tolerance test (OGTT) become relevant for clinicians.

Objective: Review of Endocrine Testing Center experience with OGTT in patients with acromegaly and in patients without acromegaly but abnormal IGF-1 levels.

Methods: Retrospective review of patients who underwent OGTT with GH measurements (Access Ultrasensitive HGH assay) between 2007-2010.

Results: 90 OGTTs were performed on 54 women and 36 men. Reasons for ordering OGTT were: mild elevation of IGF-1 (n=43, 48%), follow-up of acromegaly (n=21, 23%), combination of elevated IGF-1 levels and pituitary tumor on imaging (n=12, 13%), clinical suspicion for acromegaly (n=6, 7%), pituitary incidentaloma (n=3, 3%), elevated random GH levels (n=1, 1%) and unclear indication in 4 patients (4%). Median IGF-1 was 309 ng/ml with a median 16.6 % above age and sex adjusted normal. 43/45 patients without acromegaly suppressed GH to <0.4 ng/mL. One patient with a newly diagnosed acromegaly and 4 patients with recurrent or persistent acromegaly had a nadir GH <0.4 ng/mL (in 4/5 cases baseline secretion of GH was <1 ng/ml). Three patients in remission at the time of OGTT had a nadir GH of >0.4 ng/mL units. Sensitivity and specificity for cutoff of GH less than 0.4 ng/mL was 81% and 91%, respectively.

Conclusion: Majority (95.6%) of patients with mild elevations of IGF-1 and no acromegaly had GH suppression <0.4 ng/mL during OGTT. The proposed cutoff for GH nadir of 0.4 ng/mL provides reasonable sensitivity for diagnosis of de novo, persistent and recurrent acromegaly, but the results in acromegalic patients with low basal GH secretion should be interpreted with caution.

None of the authors have any relationships to disclose.

Poster #12

COST OF SECOND LINE NON-PHARMACOLOGIC INTERVENTIONS AND THEIR RELATED COMPLICATIONS IN CUSHING'S DISEASE: A LITERATURE-BASED ECONOMIC ANALYSIS

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Objective: To establish the direct medical costs of second line non-pharmacologic treatment strategies including a repeat transsphenoidal surgery (TSS), radiotherapy (RT), radiosurgery (RS), bilateral adrenalectomy (BLA) and related complications such as hypopituitarism (hypopit) and Nelson's syndrome (NS).

Methods: A micro-costing economic analysis from the US payer perspective was conducted based on complication rates and associated resource utilization, ICD-9 codes for surgical and inpatient costs, CPT billing codes for outpatient services/labs, and average wholesale drug prices. Sources for data included published literature, publicly available databases and radiology coding expertise. Analysis excluded monitoring and adjunct pharmacotherapy for interim control of hypercortisolemia after RT/RS. Costs reflected 2010 USD.

Results: The average one-time procedure cost for a repeat TSS, RT, RS, and BLA were \$30,000, \$29,500, \$21,600, and \$34,700, respectively. TSS complication rates varied by surgical center: CSF leak (0-18%), hypopit (14-41%), meningitis (1-8%), and thromboembolic events (0.6-6%). Adjusted costs of TSS complications based on event rates ranged from \$4,000-\$26,000 per patient. With RT/RS, approximately 50% patients can experience a loss of hormone function over time. Hypopit resulting from either TSS or RT/RS is estimated to cost \$4,400 annually. About 10-30% of patients treated with BLA experience NS (event cost of \$44,000), which when adjusted for event rates, can add an average of \$4,200-\$12,600 per patient. Including complications, total short-term direct medical costs of 2nd line non-pharmacologic interventions range from \$22,500 to \$48,000, of which the majority represented one-time costs.

Conclusion: Current second line surgical/radiological treatments in CD represent a significant economic burden, with complications adding 10-40% to the short-term cost of treatment. Future economic analyses could include long-term total costs and health-related quality of life impact of the various interventions and their associated complications.

DA Patel receives consulting fees from Novartis.

M. Maldonado is a Novartis employee.

J.M. Stephens is a Novartis employee.

S. Pulgar receives consulting fees from Novartis.

B. Swearingen has no relationships to disclose.

Poster #13

DETERMINING REMISSION IN PATIENTS WITH CUSHING'S DISEASE: A SYSTEMATIC REVIEW

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Introduction: First-line therapy for patients with Cushing's disease (CD) is transsphenoidal adenectomy (TSA) to remove an ACTH-secreting pituitary adenoma. Remission after surgery is reported as achieved in between 65-90% of patients; however, standardized criteria and tests for evaluating both short- and long-term remission have not been established.

Methods: To examine the rates and definition of remission used in various pituitary surgical centers, a systematic English language literature search (1975-present) was conducted in PubMed. The inclusion criteria were primary studies of ≥40 patients with CD that presented remission and recurrence rates after initial TSA.

Results: The search identified 46 single- or multicenter reports of remission and recurrence rates after TSA in studies of 40-620 patients with CD followed for 1-360 months post-TSA. Remission rates assessed within 2 weeks after surgery ranged from 50.5-96.6% and were defined using various combinations of biochemical tests with or without measurement of improvement in clinical parameters. Recurrence of CD occurred in 2.3-26.8% of patients and occurred 2-240 months post-TSA. Studies demonstrating hypocortisolemia post-surgery had the fewest relapses after initially successful surgery. Long-term remission occurred more often in patients with pre-surgical identification of a microadenoma versus unidentified tumors or macroadenomas. The data available did not allow a thorough comparison of the outcomes following different surgical techniques. Improvement and relapse of clinical parameters were not systematically identified.

Conclusion: The broad range of reported short- and long-term remission rates in studies of patients with CD may be due to a number of factors including: surgical skill, the criteria used to determine biochemical remission, time of post-surgical hormonal evaluation, and duration of follow-up. Standardization of biochemical assessments and systematic reporting of cortisol-dependent clinical correlates is needed.

John Newell-Price has no relationships to disclose.

Poster #14

DIABETES INSIPIDUS AND PANHYPOPITUITARISM CAUSED BY PITUITARY METASTASIS OF LUNG ADENOCARCINOMA: CASE REPORT

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Introduction: We report a rare case of diabetes insipidus caused by lung adenocarcinoma with metastasis to the posterior lobe and infundibulum of pituitary gland.

Case Report: A 54-year-old postmenopausal women presented with a 2-month history of weakness, polyuria and weight loss. Her 24-hour urine volume was 8.5 L, with a serum osmolality of 313 mOsm/kg and a urine osmolality of 169 mOsm/kg. Her urine density was 1002. A water-deprivation test was performed. Findings were consistent with central diabetes insipidus. Her anterior lobe of pituitary hormone levels were normal range initially. She was treated with daily desmopressin acetate. Pituitary MRI revealed sellar masses with infiltration of the infundibulum compatible with pituitary metastases in patient. A CT scan of her chest showed innumerable tiny nodules throughout the left lung and metastasis on right liver lobe. A bone scan revealed multiple metastatic lesions. The liver biopsy showed malign epithelial neoplasia infiltration, matching adenocarcinoma. We concluded that the DI was caused by lung adenocarcinoma which had metastasized to the hypophyseal system. Hyponatremia occurred on the following days. Laboratory blood testing showed panhypopituitarism: ACTH 6.09 pg/mL, cortisol 9.14 µg/dL, prolactin 142 ng/mL, FSH 18.88 mIU/mL, LH 0.47 mIU/mL, TSH 3.78 uIU/mL, fT4 9.1 pmol/L, GH 0.504 ng/mL, and IGF-1 126 ng/mL. Glucocorticoid and L-thyroxine replacement treatment was applied. Irradiation each to the cranium and other bone lesions was given. Erlotinib was applied. She has no evidence of progression one month after her last treatment.

Conclusion: We present a patient with sudden onset of DI, hypopituitarism and sellar masses with infiltration of the infundibulum. DI may occur in the course of some types of systemic cancer even without any other clinical symptoms or radiologic features suggesting pituitary cancer involvement.

None of the authors have any relationships to disclose.

Poster #15

DISCORDANT LEVELS OF GH AND IGF1 IN PATIENTS WITH ACROMEGALY AFTER PITUITARY SURGERY, NAIVE TO MEDICAL THERAPY AND RADIATION: IS THE PREVALENCE CHANGING WITH NEWER CONSENSUS GUIDELINES CUT-OFFS?

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Introduction: Following consensus in 2009, the criteria for acromegaly remission was tightened: normal (age/sex-adjusted) IGF, GH random <1 ug/L, and a GH nadir during OGTT of <0.4ug/L. Discordance (9.4-39%) is often attributed to somatostatin receptor ligands (SRLs) or radiation. Efficient management of patients is difficult and the relative importance of GH versus IGF1 in predicting 'control' is controversial.

Objective: Retrospectively evaluate discordant IGF-I and GH levels in acromegalic patients (naïve to other treatment) after pituitary surgery over 4 yrs at our institution.

Methods: Fifty-four consecutive patients underwent full postoperative hormonal evaluation using the same assay: GHr (Immulite 2000), OGTT and IGF-I (DPC/Siemens Immulite 2000) (medium interval 3 months, for 3 years). Twenty patients had additional 2hr 5 point GH profiles, six had repeat full evaluations using two other assays.

Results: Forty patients had concordant GHr, GHn and IGF-1 (11 controlled- diabetes mellitus). Fourteen patients had discordance: 25.9%, (4M/10F), age 44±23.4yrs, BMI 31±7.2, tumor size 1.8 ±0.9 cm, no estrogen, 2 controlled- DM. Dissociation pattern persisted (median repeated tests; 4±2). No patient had active cardiovascular disease or abnormal ECHO. Symptom score: headache, osteoarthritis, perspiration, fatigue and paresthesia was 2±2 (maximum 10). All had elevated IGF1: 1.3 ULN ±0.23. Mean±STD GH profile 0.83±0.19, GHn 0.36 ±0.14 and GHr 0.54±0.19. Pearson's correlation between IGF1 and GHr / GHn: r=-0.46 and r=-0.42 (p<0.05) and Ghn and GHr correlation r= 0.62 (P<0.01), respectively. Using GHn <0.4 and GHr<1, discordant patients decreased to ten (18.5%).

Conclusion: Discordant results were observed in approximately 20% of patients in our postoperative acromegalic patients naïve to SRLs and radiation. Interestingly, 40% had mammosomatotroph or lacto/somatotroph tumors. Using GHn of 1 or <0.5 or a 2hr GH profile did not significantly change this percentage. Patient management needs to be individualized and the clinical picture incorporated into the treatment decision with long-term studies evaluating morbidity/mortality.

None of the authors have any relationships to disclose.

EARLY MORNING CORTISOL LEVELS AS PREDICTORS OF ACUTE AND LONG-TERM ADRENAL FUNCTION AFTER TRANSPHENOIDAL SURGERY FOR PITUITARY ADENOMAS AND RATHKE'S CLEFT CYSTS

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Introduction: New long-term adrenal insufficiency after endonasal removal of pituitary adenomas or Rathke's cleft cysts (RCC) generally occurs in 5% or less of patients and is more common in adenomas over 2 cm in size. However, patients undergoing pituitary adenoma or RCC removal are often administered peri-operative glucocorticoids regardless of tumor or cyst size and even if pre-operative ACTH/cortisol levels are normal. In an effort to minimize unnecessary glucocorticoid therapy, we describe a protocol in which patients with normal pre-operative serum cortisol and ACTH levels are given glucocorticoids only if post-operative day 1 (POD1) or 2 (POD2) cortisol levels are below normal.

Methods: 207 consecutive patients undergoing endonasal surgery for a pituitary adenoma or RCC from July 2007 to December 2010 were considered for study. Of these, 68 patients with pre-operative adrenal insufficiency or Cushing's disease were excluded. Glucocorticoids were withheld unless POD1 or POD2 morning cortisol values were below normal (4-19µg/dL). Subsequent adrenal status was assessed through routine follow-up biochemical and clinical evaluations, although provocative adrenal function testing was not routinely used.

Results: The 139 patients included 119 with macroadenomas, 14 microadenomas and 6 RCCs (follow-up 3-41 months; median 10 months). Ten (7%) patients, all with macroadenomas (mean tumor diameter 29±10 mm) had subnormal morning cortisol values and were given glucocorticoids; of these 5 were weaned off within 3-28 weeks of surgery. Among 129 patients with normal POD1/POD2 cortisol values, only 2 (1.6%) were subsequently placed on glucocorticoids within 4 months of surgery. No patients experienced an adrenal crisis.

Conclusion: Normal morning cortisol values on POD1/2 after endonasal removal of a pituitary adenoma or RCC, appear to reliably predict adequate and safe adrenal function in over 97% of patients. This simple protocol avoids unnecessary peri-operative glucocorticoid therapy and poses minimal risk to the well-informed closely monitored patient.

Daniel Kelly receives royalties from and is a consultant for Mizuno-America Inc.

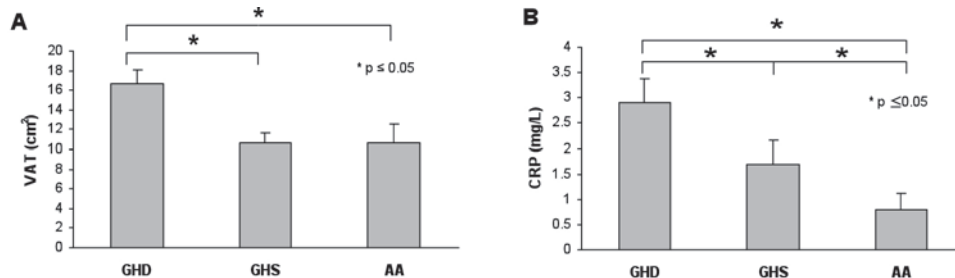
None of the other authors have any relationships to disclose.

EFFECTS OF GROWTH HORMONE DEFICIENCY ON BODY COMPOSITION AND CARDIOVASCULAR RISK MARKERS AFTER DEFINITIVE THERAPY FOR ACROMEGALY

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Objective: To determine whether development of growth hormone deficiency (GHD) after definitive therapy for acromegaly is associated with increased visceral adiposity and cardiovascular risk markers compared to GH sufficiency (GHS).



Methods: After IRB approval, we studied three groups: cured acromegaly with GHD (n=32), cured acromegaly with GHS (n=25), and active acromegaly (AA) (n=20). No patients were taking SSAs, dopamine agonists or hGH. GHD was defined as peak GH <5ng/mL (GHRH-arginine) or IGF-1 SDS <-2.0 with ≥3 pituitary deficiencies. Serum cardiovascular risk markers, carotid intima-medial thickness (IMT), and body composition were measured (by DXA and cross-sectional CT at L4).

Statistics: Fisher's Least Significant Difference Test. Means±SD are presented.

Results: Age and BMI (overall means 47±12years, 29.9±6.3kg/m², respectively) did not differ among the groups. IGF-1 SDS differed: -2.0±0.7(GHD), -1.3±0.8(GHS), and 5.1±3.5(AA) (p≤0.05). Fasting glucose (85±9 vs. 85±7 vs. 108±37mg/dL), 120-minute glucose (111±42 vs. 105±28 vs. 159±28mg/dL), HOMA-IR, fibrinogen and IMT were lower in GHD and GHS than AA (p≤0.05). Abdominal visceral (Panel A) and total adipose tissue, and total body fat (31.8±10.5 vs. 26.3±10.0 vs. 23.4±10.2kg) were higher in GHD than GHS or AA (p≤0.05). Subcutaneous abdominal fat was higher in GHD (but not GHS) than AA (p≤0.05). hsCRP (2.9±2.5 vs. 1.7±1.9 vs. 0.8±1.0mg/L) (Panel B) was highest in GHD, followed by GHS, and lowest in AA (p≤0.05). Triglycerides were lower in GHD and GHS than AA (p≤0.05). HDL was higher, and extremity lean mass lower, in GHS (but not GHD) than AA (p≤0.05). Lean body mass, mean arterial pressure, total cholesterol, and LDL were comparable among groups.

Conclusions: Insulin resistance and IMT improve after definitive treatment of acromegaly, whether GHS or GHD. Patients who develop GHD following cure of acromegaly have higher visceral adiposity and hsCRP compared with those who remain GH sufficient. Development of GHD after cure of acromegaly may adversely affect body composition and inflammatory cardiovascular risk markers.

BMK Biller receives consulting fees from NovoNordisk and Pfizer.

B Swearingen receives consulting fees from Pfizer and Novartis.

The other authors have no relationships to disclose.

Poster #18

ENDOSCOPIC SURGERY IN ACROMEGALY: EXPERIENCE IN 80 PATIENTS TREATED BY A SINGLE NEUROSURGEON

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Transsphenoidal surgery is the treatment of choice in Acromegaly. This induces remission in 50-80%. Until recently, surgical procedure was based on a microscopic transphenoidal approach. We report our experience of 80 consecutive patients with acromegaly operated with an endoscopic endonasal approach.

All data of patients operated on endoscopically of a somatotroph adenoma were reviewed. Remission was defined by GH inferior to 0.4 ng/ml after blood glucose load and normalized IGF-1 level at last follow up. Patients with clinical improvement, normal IgF1 level but abnormal GH level, without additional treatment were considered as "apparent" remission.

8 patients were lost to follow-up.

72 patients evaluated (mean follow-up = 2 years).

- 65% (n=47) of patients were in remission and 8% (n=6) in apparent remission.

Remission was achieved in 77% of cases for enclosed macroadenomas, in 84% of microadenoma, and in less than 50% in invasive macroadenomas.

This led to a total of 72% of success rate.

- 14% (n=10) were uncontrolled after surgery but controlled by medical treatments and/or radiotherapy

- 12% (n=9) remained uncontrolled despite additional treatment.

Adverse effects were observed in 7.5% of cases:

Diabetes insipidus in 3 cases, worsening of pituitary function in 2 cases, hyposmia in 1 case and sinusitis in 3 cases. No cerebrospinal leak or meningitis was observed.

Endoscopic approach is at least as effective as microscopic approach, with a low rate of adverse effects and a comparative cure rate. Endoscopy led to a better operative comfort for the surgeon and more comfortable post-operative suite for the patient. Endoscopic technique allows a better approach and view of the lateral compartment of the sella. This can facilitate resection of enclosed macroadenomas and sometimes tumoral extension in the inner compartment of the cavernous sinus. It should be the preferred surgical procedure for the treatment of acromegaly.

Henry Dufour has no relationships to disclose.

Poster #19

ESTROGEN PARTIALLY RECAPITULATES MURINE PITUITARY CELL CYCLE RESPONSE TO PREGNANCY

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As pregnancy and estrogens induce pituitary lactotroph hyperplasia, we assessed expression of pituitary cell cycle regulators in two murine models of pituitary hyperplasia, estradiol (E2) pellet implants (1.5 mg/pellet for 90 days) and pregnancy. Pituitary weights in non-pregnant mice increased 2-fold ($P < 0.001$) after 10 weeks of E2 administration, and 1.4-fold ($P < 0.001$) at day of delivery. Increased pituitary weight correlated with increased PCNA (5.5-fold, $P < 0.01$) immunostaining and protein expression at mid-late pregnancy and during E2 administration. Pituitary PCNA (~2 fold) and Ki-67 (~8 fold) mRNA levels increased during both mid-late pregnancy, and after E2 administration. Concomitant pituitary staining for prolactin and PCNA or Ki-67 showed that lactotroph cells comprised the main proliferating cell type either at mid-late pregnancy or after E2 administration. Pregnancy induced both pituitary cell cycle proliferative as well as inhibitory responses at the G1/S checkpoint. The most marked changes were observed at 2-weeks of pregnancy, at which time elevated pituitary levels of cyclin D1 and CDK inhibitors p15INK4b, p18INK4c, p19INK4d and p21Cip1 proteins were detected. Concordantly, p15INK4b and p21Cip1 mRNA levels increased 2.3- and 5.9-fold, respectively, at mid-late pregnancy. In contrast, pituitary p16INK4a and p27Kip1 protein levels were decreased. The pituitary cell cycle response to E2 administration partially recapitulated the effects observed at mid-late pregnancy, including increased expression of PCNA, Ki-67, p15INK4b and p21Cip1 levels. Pituitary cell immunostaining demonstrated increased p21Cip1 expression at mid-late pregnancy, concurrent with increased Ki-67 labeling. p21Cip1 did not co-localize in Ki-67-labeled cells. Conversely, nuclear localization of p21Cip1 was not observed during E2 administration, suggesting a pituitary cell cycle inhibitory role for p21Cip1 in pregnancy, and a possible pro-proliferative role during E2 administration. Conclusions: The murine pituitary gland meets the demand for prolactin during lactation in association with induction of both cell proliferative and inhibitory pathways mediated, at least partially, by estrogen.

None of the authors have any relationships to disclose.

Poster #20

EVALUATION OF OPERATED CUSHING'S DISEASE PATIENTS FOR DEPRESSION, LIFE QUALITY AND BODY IMAGE

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Aim: The aim of the study is to evaluate patients with Cushing's disease (CD) for depression, quality of life and body image perception by comparing with healthy controls.

Patients and Methods: Forty patients with CD and 40 healthy people matched for demographic characteristics were included to the study. Health Survey-Short Form (SF-36), Multidimensional Body-Self Relations Questionnaire (MBSRQ) and Beck Depression Inventory (BDI) were performed. Subgroups of the CD patients were formed according to their status of remission and to points they received from BDI. This study was approved by the Ethical committee of Cerrahpasa Medical School.

Results: Mean age of the CD group and control group were 39.57± 10.6 (F/M: 31/9) years and 35.66± 9.06 years (F/M: 24/16) respectively. 32 (80%) of patients with CD were under remission. There was no significance in BDI scores between the groups. Physical functioning, bodily pain, general health scores (subscales of SF-36) of the control group were significantly higher than the CD group (p= 0.003, p=0.02, p= 0.02, respectively). The mean of item scores of MBSRQ and fitness evaluation, health evaluation and body areas satisfaction scores (subscales of MBSRQ) were significantly higher in the control group than CD group (p= 0.05, p= 0.02, p= 0.002 and p= 0.003, respectively).

When CD group was evaluated according to remission, only general health score (the subscale of SF-36) was higher in the CD group with remission than the patients with CD without remission (p=0.01). The mean item score of MBSRQ, and 2 subscale of MBSRQ scores (Fitness evaluation and body areas satisfaction) was higher in the remission group than in the CD group without remission (p= 0.03, p=0.02, p= 0.03, respectively). BDI score was lower in remission group (p= 0.05).

CD group was also divided into 2 subgroups according to the BDI scores (0-16 points: non-depressive (Group1), ≥ 17 points: depressive patients (Group2)). The patients in the group 2 had lower quality of life, lower MBSRQ scores, lower SF-36 scores, less perception of body image and less body areas satisfaction than the Group 1.

Conclusion: Less quality of life, less body areas satisfaction scores and higher levels of depression were detected in the patients with CD without remission.

None of the authors have any relationships to disclose.

Poster #21

EVOLUTION OF DIAGNOSIS OF CUSHING'S DISEASE

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The difficulty in the diagnosis of Cushing disease is that the adenoma is too small to detect by radio-graphical method. Moreover, the relapse patient at long term follow up cannot be disregarded, and due to modification of fibrosis, identification of a small recurrent adenoma and the remaining tumor nest is difficult in the relapse patients.

Even if, with the aid of superconducting MRI, a morphological diagnosis of such a minuteness disease nest is done, the description rate is low (25-57%). Moreover, even if dynamic MRI were used to detect such a minute lesion, the description rate is practically the same. If super selective cavernous sinus sampling is used, it is possible to raise the presumption rate of the localization up to 81% at most. However, the method of super selective cavernous sinus sampling has a serious defect in describing accurate localization of the adenoma. In the MET-PET fusion 3T-MRI image, diagnostic accuracy which was able to make adenoma an image by elegantly visualizing vigorous activity of hormone synthesis in Cushing's adenoma was 95%. In conclusion, by MET-PET fusion 3T-MRI a revolution will be aroused both in the diagnosis and in the treatment policy of the Cushing disease.

Hidetoshi Ikeda, MD, PhD has no relationships to disclose.

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GH secretion is stimulated centrally by estradiol derived locally via aromatisation of testosterone in both men and women. In men, the inhibition of LH secretion by testosterone also requires prior aromatization to estradiol. Tamoxifen, a Selective Estrogen Receptor Modulator that blocks central estrogen action, reduces GH secretion in women¹ but not in men, at the same time increasing testosterone levels². As GH and testosterone stimulate fat metabolism, we postulated that the effect of tamoxifen in women and men may be different.

We determined whether there is a gender difference in the impact of tamoxifen on fat oxidation. Ten healthy postmenopausal women and ten healthy men were randomised to 2-week treatment with tamoxifen (20 mg/d). We measured GH response to arginine stimulation, serum levels of IGF-I, testosterone (men only), and whole body fat oxidation.

In women, tamoxifen significantly reduced the GH response to arginine stimulation (Δ -88%, $p < 0.05$) and mean IGF-I levels (Δ -23.5 \pm 5.4%, $p < 0.01$). Tamoxifen did not significantly change fasting fat oxidation but significantly reduced post-prandial fat oxidation (Δ -34.6 \pm 10.3%; $p < 0.01$).

In men, tamoxifen did not significantly change GH response to arginine stimulation but significantly reduced mean IGF-I levels (Δ -24.8 \pm 6.1%, $p < 0.01$). It significantly increased mean testosterone levels (Δ 52 \pm 14.2%; $p < 0.01$). Tamoxifen did not significantly change fasting and post-prandial fat oxidation in men.

In summary, tamoxifen attenuated the GH response to stimulation and reduced post-prandial fat oxidation in women but not in men. It increased testosterone levels in men and reduced IGF-I levels to a similar degree in both sexes.

We conclude that in therapeutic doses, the suppressive effect of tamoxifen on fat metabolism is gender dependent being greater in women than in men. As testosterone stimulates fat oxidation independently, the compensatory increase in testosterone may counteract the reduction in fat oxidation resulting from suppression of the GH-IGF-I axis activity.

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1) Birzniece et al., *J Clin Endocrinol Metab* 2010, 95: 3771-6

2) Birzniece et al., *J Clin Endocrinol Metab* 2010, 95: 5443-8

None of the authors have any relationships to disclose.

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Introduction: Gigantism is a rare disease and there is less than 100 cases reported in literature. Patients present with high stature during puberty or high growth speed. On the other hand the diagnosis can be delayed in some patients due to high familial stature.

Material: We report 7 patients harboring pituitary adenomas and gigantism.

Results: All patients were male and presented for evaluation of high stature. Median age at diagnosis was 19.2 years, median height was 1.97m and mean BMI was 26.2 Kg/m². All had macroadenoma. Median size was 2.4 cm, median basal serum GH level was 81.6 ng/ml, median serum IGF-I level was 947.8 ng/ml [471 – 1486] and median serum prolactin level was 35.2 ng/ml. No one presented multiple endocrine neoplasia. All underwent pituitary surgery and an adenoma positive for GH receptors was found in all of them; two were also positive for PRL receptors. After 12 weeks, 2 patients were under remission; in the others tumor rests were seen on MRI. Two lost follow-up and the others underwent treatment with octreotide Lar, cabergoline or pegvisomant, plus radiotherapy, with disease control.

Discussion: Treatment of gigantism has changed since new medical therapy come into clinical practice. Before 2000 radiotherapy was the treatment of choice for not cured patients, and they should wait for it effects. Nowadays, the disease can be controlled in the association of radiotherapy/medication.

None of the authors have any relationships to disclose.

Poster #24

GROWTH HORMONE SECRETORY FUNCTION IN PRIOR ACROMEGALY

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Objective: We evaluated the growth hormone secretory function and QOL of patients with prior acromegaly by comparing with patients with prior non functioning pituitary adenoma.

Subject and Method: 67 acromegaly patients (GHoma) who underwent TSS as the first treatment between January 1998 and June 2010 were studied. They met the Cortina consensus criteria for postoperative remission. Control was 99 non functioning pituitary adenoma patients (NFoma) who were performed total or subtotal excision by TSS. Both groups were evaluated their GH secretory function using ITT. QOL of GHoma was measured by SF-36.

Results: Each of severe GHD (peak GH < 1.8 ng/mL) and moderate GHD (1.8 < peak GH < 3 ng/mL) occurred in 6.0%, respectively, in our series of surgically cured acromegaly. Severe GHD occurred in 36.7% in NFoma. The frequency of GHD (peak GH < 3.0 ng/mL) was significantly lower in GHoma (12.0 %) than in NFoma (46.9%). Comparing the frequency of GHD in GHoma (20 cases) and in NFoma (26 cases) who had similar size tumor (15 - 24 mm), GHoma tended to be lower than NFoma (10.0 % vs. 30.7 %). IGF-1 levels were relatively well preserved even in GHoma with impairment of GH secretion. Patients with severe GHD tended to have low SF-36 physical component summary scores, compared to the patients with higher GH response to ITT (peak GH > 10 ng/mL).

Conclusion: As far as the prior acromegaly patients treated only by surgery, the occurrence frequency of GHD was low. But long time follow-up of their QOL, morbidity and mortality should be necessary to investigate if every acromegaly patient has to be cured for biochemically.

None of the authors have any relationships to disclose.

Poster #25

HAVE INCLUSION CRITERIA AND GROWTH HORMONE REPLACEMENT THERAPY CHANGED OVER THE LAST 15 YEARS? - AN ANALYSIS OF THE GERMAN KIMS DATABASE

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To examine the potential implications of changes in the approach to adult growth hormone (GH) replacement (GHR) over the last 15 years, we analyzed the German KIMS database as one of the largest single country pharmacoepidemiological databases on adult GH deficiency (GHD).

Based on the date of their first GH application patients were assigned to three interval groups (1995-1999, 2000-2004, 2005-2009). A MANOVA with interval and sex as independent variables was conducted. Differences were analyzed with respect to GH dose, IGF-I standard deviation score (SDS), quality of life (QoL), latency between diagnosis of GHD and first GH dose, BMI, waist-hip-ratio and lipid profile. All analyses were conducted for baseline (N=745), a one-year (N=420), and a three-year (N = 239) treatment samples.

Significant effects of time interval were found for baseline and one-year treatment data. Recently, more patients with less severe GHD (assessed by IGF-I SDS) were included in KIMS and starting GH dose decreased substantially. Patients now receive GHR three years earlier after diagnosis of GHD than 15 years ago. Normal IGF-I SDS after one year of GHR were attained until 2005. After three years of therapy IGF-I SDS had normalised in all three intervals and QoL had significantly improved. Women are treated significantly earlier after diagnosis than men. After one year of treatment women show significantly lower IGF-I SDS than men. While this suggests poorer treatment success in women, consideration of interval shows that only in the first interval women did not reach normalized IGF-I SD scores.

Patients in KIMS Germany today are clearly different from those included in earlier years. These prominent changes in patient characteristics and handling of GHR affect research directly as current trends can be obscured by a previous bias. Thus, future studies should consider date of inclusion as a confounding variable.

Ilonka Kreitschmann-Andermahr, Georg Brabant, Harald Jörn Schneider and Henri Wallaschofski receive consulting fees from Pfizer.

Georg Brabante, Ilonka Kreitschmann-Andermahr, Harald Jörn Schneider, and Henri Wallaschofski receive consulting fees from Pfizer.

Flverly Francis and Sonja Westermann have no relationships to disclose.

IMPROVEMENT IN CLINICAL SIGNS AND SYMPTOMS OF CUSHING'S DISEASE DURING 12 MONTHS OF PASIREOTIDE THERAPY

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Introduction: The multireceptor-targeted somatostatin analogue pasireotide has demonstrated efficacy in reducing cortisol in patients with Cushing's disease in a large, randomized, double-blind, Phase III study; the effects of pasireotide on signs/symptoms of Cushing's disease were investigated as secondary objectives.

Methods: Following ethical committee approval, patients with persistent/recurrent or de novo Cushing's disease were randomized to pasireotide 600µg (n=82) or 900µg (n=80) sc bid for 12 months. Dose increases of 300µg bid were permitted after month 3 depending on 24-hour urinary free cortisol (UFC) levels. Dose decreases based on AEs were also allowed. Clinical signs and symptoms of Cushing's disease were evaluated at regular intervals. Health-related quality of life (HRQoL) was assessed using the CushingQoL questionnaire.

Results: Median percent change in UFC from baseline to month 6 was -47.9%. Significant improvements in systolic (SBP) and diastolic blood pressure (DBP), LDL-cholesterol, weight and HRQoL were seen during 12 months' pasireotide therapy. In the overall population, the mean (95%CI) changes from baseline to month 6 were: SBP -9.1mmHg (-12.3, -5.8), DBP -4.6mmHg (-6.9, -2.3), LDL-cholesterol -0.3mmol/L (-0.5, -0.1), weight -4.4kg (-5.2, -3.5), HRQoL score 9.5 (6.6, 12.4). At 12 months, the mean changes from baseline were: SBP -6.1mmHg (-9.8, -2.4), DBP -3.7mmHg (-6.2, -1.2), LDL-cholesterol -0.4mmol/L (-0.6, -0.2), weight -6.7kg (-8.0, -5.4), HRQoL score 11.1 (6.8, 15.5). Improvements in facial rubor, supraclavicular and dorsal fat pad were also observed (photographically assessed by a blinded reviewer at each site). These clinical changes were achieved regardless of whether UFC normalized. Adverse effects were typical of somatostatin analogues, except for hyperglycemia.

Conclusion: Significant improvements in the symptoms of Cushing's disease were seen during 12 months' pasireotide treatment. These improvements were not dependent on UFC normalization, suggesting a reduction in UFC can be associated with significant clinical benefit.

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R. Pivonello, LR Salgado, and F Gu have no relationships to disclose.

This abstract includes discussion of products unlabeled for use as approved by the FDA / equivalent regulatory authority in the country in which the study/trials were performed.

INITIAL HYPOTHALAMIC INVOLVEMENT IS THE MAJOR RISK FACTOR FOR IMPAIRED PROGNOSIS AND QUALITY OF LIFE IN CHILDHOOD CRANIOPHARYNGIOMA REGARDLESS OF CHOSEN TREATMENT STRATEGIES – RESULTS OF KRANIOPHARYNGEOM 2000

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Hypothalamic obesity has major impact on quality of life (QoL) in childhood craniopharyngioma. The pathogenic relevance of initial hypothalamic involvement versus treatment-related hypothalamic lesions is a matter of controversy.

120 patients were recruited prospectively (2001-2007) and evaluated after 3 years of follow-up. Body mass index (BMI) and QoL at diagnosis and 36 months after diagnosis were analyzed based on reference assessment of tumour localization and post-surgical hypothalamic lesions using a standardized grading system (no, anterior, posterior involvement/lesion). Treatment was analyzed regarding strategy of 50 participating neurosurgical centres and the centre size. Based on patient load during the 6-year recruitment period, centres were categorized as small (1 patient/6 yrs), middle (2-5 patients/6 yrs) or large-sized centres (>5 patients/6 yrs).

BMISDS at diagnosis was similar in patients with/without hypothalamic involvement. Surgical lesions of anterior/posterior hypothalamic areas were associated with increases in BMISDS during 36 months post-diagnosis compared to patients without or only anterior lesion (+1.8BMISD, p=0.033; +2.1BMISD, p=0.011), negatively impacting QoL in patients with posterior hypothalamic lesions. Surgical strategies varied between the 50 centres (3 large, 24 middle-sized, 23 small centres). Patients treated in small centres presented with a higher rate of hypothalamic involvement compared to middle- and large-sized centres. Treatment in large centres was less radical, the rates of complete resection and hypothalamic surgical lesions lower than those of middle-/small-sized centres. However, a multivariable analysis showed that pre-operative hypothalamic involvement was the only independent risk factor for severe obesity (p=0.002).

Strategies leading to posterior hypothalamic lesions are not recommended due to potential to exacerbate hypothalamic obesity and impaired QoL. Because our results show that initial hypothalamic involvement has an a priori effect on the clinical course, our recommendations are based on recognizing craniopharyngioma as a chronic disease requiring experienced multidisciplinary teams in order to provide the best lifetime QoL for the patient.

None of the authors have any relationships to disclose.

Poster #28

LONG-TERM TREATMENT OF ACROMEGALIC PATIENTS NOT CURED AFTER TRANSESPHENOIDAL SURGERY

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Introduction: Acromegaly is a rare disease and can be cured by surgery in 50% of patients with macroadenoma and in 90% of those with microadenoma. Clinical treatment includes the use of drugs such as somatostatin analogs and antagonists of GH receptor and radiotherapy. Uncontrolled, acromegaly has increased mortality rate due cardiovascular disease, which is directly related to GH excess.

Objective: To report the long term management of acromegalic patients not cured after transsphenoidal surgery (TSS) or who refused surgery.

Patients and Methods: We evaluated 20 patients (7 male). Age at diagnosis was 41 + 11 years old. Acromegaly was caused by pituitary macroadenoma in all patients. Mean tumor size was 2.6 + 1.2 cm. Nineteen patients underwent TSS, and one refused surgery. Results are shown in mean + standard deviation (SD) and were considered statistically significant if $p < 0,05$ (Fisher's Exact test).

Results: The duration of follow up after surgery was 8.5 + 4.9 years. Serum basal level of GH was 66,9 + 95,4 ng/ml, IGF-I was 871,2 + 414,0 ng/ml, SD IGF-I age-dependent + 1.2. Before TSS cortisol, thyroid and sexual hormonal deficiency were observed in 8%, 17% and 25% of the patients, and after TSS in 40%, 35% and 50% of them. Diabetes mellitus, hypertension and dyslipidemia were present in 59%, 65% and 31% of the patients before TSS and in 55%, 50% and 80% ($p < 0,05$) of them after surgery. After unsuccessful TSS all patients were treated with octreotide LAR. Seventy-five percent of the patients responded to octreotide LAR, pegvisomant was added to those who didn't achieve the ideal control of IGF-I. Radiotherapy was performed in 78% of the patients. At the end of follow up GH – 6.7 + 7.8 ng/ml, IGF-I – 279,1 + 214,3 ng/ml, SD IGF-I age-dependent – 0,0.

Conclusion: Long-term treatment with octreotide LAR alone or associated with pegvisomant or radiotherapy was successful in almost all patients with acromegaly after failed surgical treatment.

None of the authors have any relationships to disclose.

Poster #29

MONOCLONAL ANTIBODIES FOR THE TREATMENT OF LYMPHOCYTIC HYPOPHYSITIS: CASE REPORT OF DURABLE REMISSION FOLLOWING RITUXIMAB AND LACK OF RESPONSE TO INFlixIMAB

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Objective: To report the lack of efficacy of Infliximab and durable response to Rituximab in a case of lymphocytic hypophysitis.

Methods: Clinical features, laboratory results, MRI characteristics and pathology findings were reviewed.

Results: A 52 year old woman presented with uveitis, facial palsy and obtundation. Endocrine evaluation was consistent with panhypopituitarism and diabetes insipidus. MRI revealed an enlarged pituitary with thickening of the stalk and enhancement of the surrounding dura. Tests for autoimmune and infectious etiologies were negative with the exception of positive ANA. Lumbar puncture was unremarkable with negative PCR, AFB and fungal cultures. For a presumptive diagnosis of neurosarcoidosis three doses of solumedrol, 1gram IV and Infliximab 200 mg IV were administered. Repeat MRI in three weeks demonstrated improvement. After completing the Infliximab load, treatment continued with Infliximab 5mg/kg every eight weeks, oral prednisone and methotrexate. After 6 months of this regimen the patient developed worsening headaches and vision loss. MRI revealed bilateral optic neuritis and recurrence of pituitary enlargement. Trans-sphenoidal biopsy revealed lymphocytic hypophysitis with a predominance of B lymphocytes. Treatment with the anti-CD20 monoclonal antibody Rituximab at a dose of 1 gram IV was initiated. Following two courses of Rituximab, prompt resolution of MRI findings and inflammatory markers was documented and glucocorticoids were discontinued. Biochemical testing demonstrated recovery of the HPA axis, though secondary hypothyroidism and diminished gonadotroph function persisted. At the time of this report the patient has been in clinical remission and has not required further courses of glucocorticoids or Rituximab during thirty months of followup.

Conclusion: This is the first case report describing treatment of lymphocytic hypophysitis with Infliximab and Rituximab. Rituximab may be an effective treatment option for lymphocytic hypophysitis.

Neither author has any relationships to disclose.

This abstract includes discussion of products unlabeled for use as approved by the FDA / equivalent regulatory authority in the country in which the study/trials were performed.

OROFACIAL EVALUATION IN PATIENTS WITH ACROMEGALY

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Introduction: Acromegalic patients often have craniofacial alterations such as mandibular prognathism, soft tissue increase and occlusion changes. These conditions cause chewing disorders, joint and muscle pain, speech difficulties and aesthetic problems that decrease quality of life.

Objective: Evaluate the orofacial features of acromegalic patients.

Methods: Anamnesis, facial, oral and pantomographic assessment were performed in 44 patients (26 women) with mean age of 48 years. This study was approved by the Ethics Committee of the University of Sao Paulo School of Medicine.

Results: The following data were found:

Face: Enlargement of the nose and prominent forehead (61%), facial asymmetry (63%), lips thickening (57%) and prominent menton (34%).

Oral cavity: patients partial dentulous (82%), anterior crossbite (47%), high DMFT (decayed, missing and filled teeth) index– 21.68, high periodontal index (44%) and presence of infection (75%).

Pantomographic analysis (n=34): enlargement and/or lengthening of the lower jaw's condyles (85%) and bone condensation in lower jaw goniac angle (61%).

Associated diseases: hypertension (61%), type 2 diabetes (57%) and sleep apnea (50%).

Conclusions: A high percentage of oral infections and alterations in orofacial features were observed. The presence of oral infection associated with high prevalence of type 2 diabetes mellitus impairs patient's clinical conditions. Participation of the dentist in a medical team becomes essential in order to provide oral and systemic health to acromegalic patients. Orthodontist and orthognathic surgeon together could provide occlusion and facial corrections at the appropriate moment. Multidisciplinary team may lead to quality of life improvement in these patients.

None of the authors have any relationships to disclose.

Poster #31

OUTCOME AFTER TRANSPHENOIDAL TRANSTUBERCULAR APPROACH FOR SUPRADIAPHRAGMATIC CRANIOPHARYNGIOMAS: A RETROSPECTIVE STUDY OF 33 CONSECUTIVE MONOCENTRIC CASES

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Suprasellar craniopharyngiomas remain challenging tumors. We have used the transphenoidal transtuberular approach to resect selected cases of craniopharyngiomas.

From June 2002 to December 2010, 33 supradiaphragmatic craniopharyngiomas have been operated upon by extended transtuberular transphenoidal approach (HD). This represents 75% of the supradiaphragmatic craniopharyngiomas that were operated on in our department in the same period of time. Patients were aged 18 to 70. Mean tumor diameter was 25 mm (15-35). All tumors were identified as infrachiasmatic and supradiaphragmatic on the preoperative MRI. Before operation, 29 patients had visual disturbance (87%), 21 patients had at least one pituitary deficiency (64%). Nine patients (29%) presented diabetes insipidus. 18 patients (54%) had visual deficit and pituitary deficiency.

The resection was total in 27 (81%), near total in 4 (13%) and partial in 2 (6%). Mean operative time was 100 mn. There was one postoperative death due to subarachnoid hemorrhage. Mean hospital stay was 8 days (3 to 55). Follow up was 6 to 101 months (M=29). Patients with preoperative visual deficit were normalized in 16 cases (57%), improved in 6 (21%), unchanged in 4 (15%), worsened in 2 (7%). 95% of patients had postoperative pituitary deficiency and all (100%) had postoperative diabetes insipidus despite preservation of the pituitary stalk in 3 cases (9%). 5 (15%) had postoperative rhinorrhea, 3 (9%) had meningitis, one had memory disturbance. There were 3 (9%) recurrences at 4, 24 and 60 months.

This series demonstrates that selected cases of entirely suprasellar craniopharyngiomas can be resected with an extended transphenoidal approach. Visual results are excellent due to the lack of manipulation of the optic pathway. In this series, hormonal results are bad but need to be compared with the intracranial approach. The mean problem is post-operative meningitis and rhinorrhea.

Henry Dufour has no relationships to disclose.

Poster #32

OUTCOME OF DOPAMINE AGONISTS IN MEN WITH MACROPROLACTINOMAS

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The available data indicate that valvulopathic effect of CAB depends on a cumulative dose in patients with prolactinomas. Whether lower doses of CAB are also associated with significant valvulopathy is unknown and present a dilemma to endocrinologists managing such patients. The aim of this retrospective study is to observe the medical management, and treatment outcomes of male with macro and giant prolactinomas.

Twenty two patients, median age of 45yr (20-67yr) at diagnosis, managed with DAs therapy alone for at least 1 year were included. At presentation, median PRL was 1228ng/ml (250-10382), and the mean maximal tumor diameter was 29.13±10.10mm(14-55). Pretreatment echocardiographic examination of the patients was not available at that time. The most recent hormonal values, MRI, and echocardiographic examination were reported for clinical endpoint in an individual patient. All patients were followed for a mean of 63.8months (12-149). Thirteen had visual field defect (59.1%), 16 had hypogonadism (72.2%), 4 had hypothyroidism (18.2%), and 8 had hypocortisolism (36.4). The mean maintaining dose (range) of BRC and CAB were 4.06±1.86mg daily (2.5-7.5), and 0.96±0.61mg weekly (0.25-2.0), respectively. The patients noted marked improvement in sexual function within 2-3 months of therapy. PRL and visual field defect normalized in all. During follow-up period, a subset of patients required testosterone (27.3%), thyroid (13.6%), and glucocorticoid (13.6%) replacement therapy. The mean tumor shrinkage was 61.85±25.14% (20-100%). Three macroprolactinomas disappeared, however, one of them and another 2 patients have not been taking therapy for 56.7±1.5months (55-58). At the latest control, first echocardiographic evaluation showed no valvulopathy under DAs in all of the patients.

As a result, we did not detect an increased risk for clinically relevant valve regurgitation or changes in valve morphology with mean cumulative doses of 134mg CAB, and 7542mg BRC.

In conclusion, clinicians should recommend the lowest possible doses of dopamine agonists and address the question of echocardiographic monitoring on an individual basis.

None of the authors have any relationships to disclose.

Poster #33

PATHOLOGIC AND CLINICAL FEATURES OF PITUITARY ADENOMAS SHOWING TSH IMMUNOREACTIVITY (IR)

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In addition to thyrotropinomas, clinically non-functioning adenomas and somatotropinomas may show TSH IR. It is unclear whether TSH IR in these adenomas is associated with specific phenotypic features.

To examine the relationship between TSH IR and phenotype, records of all patients undergoing pituitary surgery between 1999-2009 at one institution were searched (N=1223), and 166 patients identified, whose tumors showed TSH IR. Thirty tumors showed TSH IR in many/most tumor cells (MM), and 136 showed TSH IR in rare/some tumor cells (RS). All patients were individually matched with 166 controls whose tumors showed no TSH IR (NN).

Population characteristics (N=332): age (mean±SD): 51.5±15.1 yr; gender: 150 women, 182 men; tumor size: 23±9 mm (8 microadenomas, 324 macroadenomas). Thirteen patients had hyperthyroidism (including 9 with non-suppressed serum TSH), 14 patients had goiter, 56 patients had acromegaly, 126 patients had visual field defects, and 10 patients had pituitary apoplexy.

Stratified by TSH IR (MM, RS, NN), there was an association between IR for TSH and FSH (93%, 79 %, 29 %, P<0.0001), LH (89%, 81%, 22%, P<0.0001), alpha subunit (100%, 85%, 29%, P<0.0001), and GH (54%, 28%, 22%, P=0.0036), but not prolactin or ACTH. In the subgroup of acromegalic patients there were associations between TSH IR and IR for FSH (P<0.0001), LH (P<0.0001), and alpha subunit (P<0.0001), but not prolactin or ACTH. Patients with TSH IR tumors were more likely to have hyperthyroidism (36%, 23%, 12%, P<0.0001) and goiter (14%, 23%, 4%, P=0.0179) but less likely to have pituitary apoplexy (0%, 1%, 5%, P=0.0429).

In conclusion, patients with pituitary adenomas showing TSH IR were more likely to have IR for FSH, LH, GH, alpha subunit and were more likely to have hyperthyroidism and goiter, but less likely to have pituitary apoplexy. These results suggest a relationship between TSH IR and specific phenotypic features.

None of the authors have any relationships to disclose.

Poster #34

POSSIBLE ROLE FOR IGF-1 IN THE CONTROL OF NON FUNCTIONING PITUITARY ADENOMAS CELL GROWTH

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The main therapeutic approach for non functioning pituitary adenomas (NFA) is surgery, since radiotherapy has several important side effects and medical therapy is rarely effective. Therefore, understanding the molecular pathways regulating NFA cell proliferation is crucial for future drug development. We here explore the possible role of Insulin-like Growth Factor-1 (IGF-1) in regulating NFA cell growth in primary culture. To this aim 10 NFA primary cultures were incubated with or without IGF-1 in the presence or in the absence of Everolimus, an mTOR inhibitor, which down-regulates IGF-1 signalling through the PI3K/Akt pathway. IGF-1 significantly enhanced NFA cell viability, an effect completely blocked by Everolimus. Co-incubation with an IGF-1 receptor blocking antibody enhanced the antiproliferative effects of Everolimus. Phosphorylation of p70S6K, a down-stream effector of mTOR in the PI3K/Akt pathway was as well enhanced by IGF-1 and reduced by Everolimus, indicating that IGF-1 exerts its proliferative effects by inducing this pathway, which, in turn, can be effectively blocked by Everolimus. In conclusion, our results indicate that IGF-1 directly stimulates NFA cell viability through its own receptor. This effect is blocked by Everolimus, which may represent a new therapeutic approach for NFA.

None of the authors have any relationships to disclose.

Poster #35

PROLACTOMEGALY: TREATMENT OF A UNIQUE DUAL PITUITARY ADENOMA WITH PASIREOTIDE

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We describe a unique case of dual pituitary adenomas, one secreting growth hormone (GH)/prolactin and the other prolactin, and their response to pasireotide.

A 33 year old woman was found to have hyperprolactinaemia of 3776 mIU/L (50-500 mIU/L) and an elevated IGF-1 of 1.7 U/ml (0.4-1.6 U/ml) during investigations for amenorrhoea in 2005. MRI showed two pituitary adenomas, 9mm in the left-lobe and 6mm in the right-lobe.

Cabergoline treatment (2mg/week) resulted in prolactin normalisation and a decrease in size of the left-sided adenoma six months later to 3mm. IGF-1 remained elevated at 2.1 U/ml. Lanreotide (60mg/month) was added and IGF-1 fell to 1.1 U/ml after twelve months, with no significant change to the right-sided adenoma.

Cabergoline and lanreotide were stopped on confirmation of pregnancy in 2006. Three months post-partum, prolactin was 2216 mIU/L and IGF-1 was 1.7 U/ml. This correlated with pituitary MRI that showed further increase in size of right adenoma to 11 mm. Throughout 2007 to 2009, she was treated with cabergoline with satisfactory control of hyperprolactinaemia and no reappearance of left sided pituitary adenoma.

During this time, patient refused lanreotide and oral contraceptive pill was used for dual purpose of contraception and for acromegaly control. IGF-1 was maintained within the normal range.

In 2010, patient was given a therapeutic trial of pasireotide. Cabergoline was stopped twelve months prior to pasireotide trial. Baseline pituitary MRI prior to trial of pasireotide showed further increase in the right pituitary adenoma to 14mm. Following 9 months of therapy, size of adenoma decreased and biochemical control of hyperprolactinaemia and acromegaly was sustained.

In summary, we describe a rare patient harbouring two pituitary adenomas, the left adenoma secretes prolactin, and the right, GH and prolactin. Its therapeutic response to a new generation somatostatin analogue illustrates the efficacy of pasireotide towards secretory adenomas.

None of the authors have any relationships to disclose.

This abstract includes discussion of products unlabeled for use as approved by the FDA / equivalent regulatory authority in the country in which the study/trials were performed.

Poster #36

RANDOMIZED MULTICENTER TRIAL ON PATIENTS WITH CHILDHOOD CRANIOPHARYNGIOMA (KRANIOPHARYNGEOM 2007) – UPDATE AFTER 41 MONTHS OF RECRUITMENT

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Despite high survival rates (92%) in patients with childhood craniopharyngioma (CP), quality of life (QoL) is frequently impaired due to sequelae such as severe obesity resulting from hypothalamic involvement of CP. Based on the results of the multicenter prospective study KRANIOPHARYNGEOM 2000 radical surgery is no appropriate treatment strategy in patients with hypothalamic involvement. Furthermore, tumour progression/relapses are frequent early events in CP patients. The analysis of event-free survival-rates (EFS) in 117 prospectively evaluated patients with CP showed a high rate of early events in terms of tumour progression after incomplete resection (EFS: 0.31±0.07) and relapses after complete resection (EFS: 0.63±0.09) during the first three years of follow-up.

Accordingly, in KRANIOPHARYNGEOM 2007 QoL, and survival rates in CP pts (>5yrs at diagnosis) are analyzed after randomization of the time point of irradiation (XRT) after incomplete resection (immediate XRT versus XRT at progression of residual tumour). Up to now (03/11) 78 pts with CP were recruited (42 pts in the randomization arm; 33 pts in the surveillance arm; 3 pts in the process of review of imaging). 13 of 42 pts were randomized. 29 pts could not be randomized due to parental decision (11 pts), late schedule (14 pts) and due to decision of the physician (4 pts).

In conclusion, KRANIOPHARYNGEOM 2007 represents the first randomized trial in CP and the first study in pediatric neurooncology analyzing QoL as an endpoint. Aim of the study is to analyze the appropriate time point of XRT in order to improve QoL in patients with hypothalamic involvement. The recruiting compliance is high. However, the randomization compliance has to be improved in order to reach cohort sizes necessary for reliable statistical analysis and to answer the questions assessed by the randomized trial KRANIOPHARYNGEOM 2007.

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None of the authors have any relationships to disclose.*

Poster #37

RATHKE'S CLEFT CYST APOPLEXY - THE SIGNIFICANCE OF ASSOCIATED HYPOPHYSITIS: CASE REPORT

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Introduction: Rathke's cleft cysts (RCC) have been associated with secondary hypophysitis as a result of rupture of their lining. However, in the context of a hemorrhagic RCC (RCC apoplexy), the interpretation of adjacent pituitary inflammation and its significance may be challenging.

Methods: We describe a case of RCC apoplexy associated with hypophysitis that then recurred.

Results: A 25 yr-old woman presented in her 30th week of pregnancy with 4 weeks of worsening headaches. MRI revealed a 20 mm cystic and solid sellar mass with suprasellar extension. The cystic changes and high signal on the T1WI were suggestive of subacute/chronic hemorrhage and the contents of a RCC. Hormonal studies revealed central hypothyroidism and mildly elevated prolactin levels. Via an endonasal transphenoidal approach, a firm rubbery pale mass was encountered which proved to be inflamed anterior pituitary gland. Upon incising the cystic portion of the lesion, fluid poured forth consistent with a RCC. Final pathology confirmed RCC with acute and chronic inflammation of the anterior pituitary gland. The patient was treated with a tapering steroid regimen and had an uneventful pregnancy and has remained on maintenance steroid. Three years later, she presented again with worsening headaches. Clinical presentation and MRI findings were consistent with recurrent RCC with apoplexy; repeat endonasal surgery was undertaken and pathology again confirmed RCC lining with acute and chronic inflammation. Six months after surgery she is doing well.

Conclusion: Apoplectic RCCs are relatively rare and etiology of the initial hemorrhage is unclear. This case of a recurrent RCC with hypophysitis appears to demonstrate that in the setting of a hemorrhagic RCC, blood products may induce a severe acute and chronic inflammatory cell infiltrate. Whether the partial rupture of the RCC contents into or along the anterior pituitary gland is also partially responsible for inciting hypophysitis is unclear.

None of the authors have any relationships to disclose.

Jung Hee Kim

*Division of Endocrinology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea***Context:** There are few studies which have analyzed the long-term recurrence rates of Cushing's disease after trans-sphenoidal surgery.**Methods:** A retrospective chart review of Cushing's disease patients treated with trans-sphenoidal surgery from 1984 to 2010 at Seoul National University Hospital was performed. A total of 54 patients were included for analysis. Recurrence was defined as an elevated serum cortisol, an elevated 24 hr urine free cortisol or a dexamethasone suppression serum cortisol higher than 5µg/dl. Serum cortisol, serum ACTH, 24 hour urine free cortisol, result of imaging studies and pathologic findings were analyzed.**Results:** Among 54 patients, there were 41 female patients. Mean age at diagnosis was 35.8 ± 12.8 years and mean follow-up duration was 102.6 ± 60.0 months. Initial successful trans-sphenoidal surgery was obtained in 39 patients (72.2%). Among these 39 (72.2%) patients, 18 (46.2%) patients had a recurrence of Cushing's disease. Postoperative serum cortisol level and 24 hour urine free cortisol after surgery was higher in patients with persistence than with initial remission. Preoperative serum cortisol was significantly associated with a recurrence ($P = 0.048$). Pathologic confirmation of an adenoma was marginally associated with lower risk of a recurrence ($P = 0.057$).

Positive results of image study and presence of microadenoma were not associated with risk of recurrence.

Conclusions: Recurrence rate of Cushing's disease after initial successful trans-sphenoidal surgery was 46.2%. Preoperative serum cortisol level and pathologic confirmation of an adenoma had a predictive value for recurrence of Cushing's disease after trans-sphenoidal surgery.*Jung Hee Kim has no relationships to disclose.*

RESPONSE TO PEGVISOMANT OR PEGVISOMANT PLUS SOMATOSTATIN ANALOGUES TREATMENT AND GROWTH HORMONE RECEPTOR GENE POLYMORFISMS IN ACROMEGALIC PATIENTS: A MULTICENTER STUDY

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Aim of the study was to evaluate the influence GHR polymorfisms in acromegalics, treated with Pegvisomant (Peg) alone or combined with somatostatin analogues (SSA). A multicenter cross-sectional pharmacogenetic study was set up including 127 patients from 16 Italian Endocrinology Centers. All patients were clinically described and genotyped for d3, rs348388342, rs6413484, rs6181, rs6180 and rs35395580 GHR polymorfisms. 64 patients received Peg+SSA therapy.

Only d3 showed allele frequencies suitable for statistical analysis while rs348388342, rs6413484, rs6181 and rs35395580 GHR polymorfisms did not showed significant variability and excluded from the study. 18 patients (13,9%) were d3-GHR homozygotes, 41 (34,3%) heterozygotes, and 68 (51,9%) were homozygotes for full-length GHR (fl-GHR). Allele frequencies were not significantly different from those observed in normals and non-Peg treated acromegalics, although the lack of Hardy-Weinberg equilibrium was observed. Peg dosage was not different between d3 and fl-GHR patients, either in the whole set or in Peg (1.3 ± 0.42 vs 1.5 ± 0.6 , $P=0.396$) and Peg+SSA (1.2 ± 0.4 vs 1.3 ± 0.7 , $P=0.482$ in Peg + SSA) groups. Finally, no association between d3 or rs6180 genotypes and adverse effects or tumor residue growth was observed. Stepwise linear regression analysis excluded d3 and rs6180 from predictors of Peg dosage.

In conclusion, d3 GHR polymorphism is not associated with lesser Peg dosage both in monotherapy and combined treatment groups. Further studies could clarify if lack of Hardy-Weinberg equilibrium may be a random effect or due to a role of d3 in the seriousness of the disease activity.

None of the authors have any relationships to disclose.

RESULTS OF LONG-TERM TREATMENT (6 YEARS) WITH THE MULTIRECEPTOR-TARGETED SOMATOSTATIN ANALOGUE PASIREOTIDE IN A PATIENT WITH CUSHING'S DISEASE (CD)

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Introduction: A multicenter, Phase II, proof-of-concept trial previously showed that 15 days' treatment with the multireceptor-targeted somatostatin analogue pasireotide decreased urinary free cortisol (UFC) levels in 22/29 patients with CD. Here we report 6 years' follow-up of a patient enrolled in this trial (conducted according to the Declaration of Helsinki).

Results: In February 2004, a 43-year-old woman was referred for CD with truncal obesity, weight gain (11kg in 6 months) and UFC 12.4x upper limit of normal (ULN). IPSS confirmed pituitary disease. In July 2004, with UFC 9.2xULN, the patient began 15 days' treatment with subcutaneous pasireotide 600µg bid, resulting in UFC normalization (0.75xULN; 92% reduction). Pasireotide administration was then halted until enrollment in the extension phase of the trial 35 days later, during which time her UFC increased to 3.3xULN. In September 2004, she resumed pasireotide 600µg bid, showing clinical improvements including 13kg weight loss and improvement in hirsutism, supraclavicular fat pads and facial erythrosis; however, hyperglycemia was observed (fasting glucose 5.9–7.7mmol/L, HbA1c 5.7–7.7%) without anti-diabetic treatments. Between 2006 and 2011, her LDL-cholesterol level decreased from 1.8 to 1.3g/L, with slight improvements in lumbar and femoral T scores (–1.7 to –1.5 and –1.9 to –1.6, respectively). Asthenia occurred at very low UFC levels, and pasireotide dose was reduced to 450µg bid from November 2004 to October 2005, during which time her UFC levels were generally >ULN. Since November 2005, she has been treated with pasireotide 600µg bid, with normalized UFC levels seen in the majority of monthly assessments and moderate reduction in basal and desmopressin-stimulated ACTH levels.

Conclusion: This case illustrates the long-term efficacy of subcutaneous pasireotide in controlling CD without escape. No serious side effects were observed; however, despite good UFC control, alterations in glucose tolerance should be carefully monitored.

Xavier Bertagna is on a Novartis advisory committee.

Jérôme Bertherat is a speaker for Novartis and a consultant for Merck Serono.

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Gareth Hughes is a Novartis employee.

Mario Maldonado is a Novartis employee.

Rossella Libé, Camille Baudry, Bruno Donadille, Lionel Groussin, and Laurence Guignat have no relationships to disclose.

This abstract includes discussion of products unlabeled for use as approved by the FDA / equivalent regulatory authority in the country in which the study/trials were performed.

SIGNIFICANT BURDEN OF ILLNESS IN PATIENTS WITH CUSHING'S DISEASE

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Background: Cushing's disease (CD) is caused by an adrenocorticotrophic hormone-secreting pituitary adenoma. The subsequent overproduction of cortisol leads to the characteristic features of CD and significant clinical comorbidities.

Methods: A literature review was conducted to assess the holistic burden of CD, encompassing epidemiology, morbidity, mortality and treatment outcomes. Articles published between 2000 and 2009 in Medline, EMBASE and Science Citation Index were searched, along with bibliographies of retrieved articles.

Results: Patients with CD have a significantly worse health-related quality of life (HRQoL) than age- and sex-matched controls (Table). Mortality rates are 1.7- to 3.7-times higher than age-adjusted rates, while persistent hypercortisolism is associated with an even higher standardized mortality risk (SMR=4.4). Cardiovascular disease is the leading cause of death. Remission rates for transsphenoidal surgery (TSS) are 65-90% when performed by expert pituitary surgeons. Relapse rates after TSS (5-36%) increase with the length of follow-up. 20-30% of adenomas cannot be localized, which is implicated as a predictor of poor outcomes. Second surgery and pituitary irradiation are associated with increased risk of hypopituitarism (50% and 13-56%, respectively). Bilateral adrenalectomy is highly effective (95% remission) but increases the risk of Nelson's syndrome (15-46%), reduces HRQoL, and requires lifelong replacement therapy. The efficacy of available medical treatments is limited and these pose additional toxicity risks.

Conclusion: The burden of CD is significant and encompasses increased mortality and morbidity, and has a severe impact on HRQoL. Existing treatment options are limited, and new medical treatments directly targeting the pituitary adenoma (the underlying cause of the disease) could help address the persistent unmet needs in CD.

Table. Characteristics of patients with CD

Characteristic	Range
Incidence of CD, per million	0.7-2.4
Time from onset to diagnosis, years	2.5-5.0
Comorbidity at diagnosis, %	
Hypertension	58-85
Obesity	20-41
Diabetes mellitus	20-50
Major depression	50-80
Osteoporosis	30-50
Hyperlipidemia	60-70

SJ Pulgar is a Novartis employee.

RA Feelders, and A Kempel have no relationships to disclose.

SILENT CORTICOTROPINOMA: REPORT OF FIVE PATIENTS

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Introduction: Pituitary tumors are the most prevalent benign neoplasias among those within the central nervous system. Non-secreting adenoma (NSA) represents 40% of them and immunohistochemistry findings showing expression of LH and FSH receptors are the most common. Less frequently, these tumors could be positive for ACTH or GH receptors, and might represent silent corticotropinoma (SCT) or somatotrophinoma.

Methods: We report five patients harboring SCT (1 male).

Results: Median age at diagnosis was 47 years; median BMI was 32kg/m². Clinical presentation included headache in two patients, visual loss in one, amenorrhea in one and a cerebral aneurysm in one patient. No one showed any physical finding suggesting Cushing's Syndrome. At presentation, one patient had non-insulin-dependent diabetes mellitus, three had hypertension and all five had dyslipidemia. Pituitary tumors were macroadenoma with median size of 2.9 cm; basal cortisol and ACTH were within the normal range. All underwent pituitary surgery and got pathological findings revealing adenoma with immunohistochemistry positive for ACTH receptors. After surgery, one patient was cured, and four had residual tumor in the follow-up MRI; three developed adrenal insufficiency. After surgery, body weight decreased in all patients and the patient with visual loss recovered vision.

Median follow up was 2.7 years, and the median urinary free cortisol – 68,1 mcg/24h

Conclusion: Evaluation for hypercortisolism in NSA can be helpful before surgery. SCT usually present in a more aggressive manner than NSA, and instead they express ACTH, patients can evolve with adrenal insufficiency.

None of the authors have any relationships to disclose.

SLOW DECLINATION OF THE IGF-1 OVER A YEAR AND LATE NORMALIZATION OF NADIR GH AFTER TRANSSPHEOIDAL ADENOMECTOMY OF GH PRODUCING PITUITARY ADENOMAS

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Introduction: Postoperative IGF-1 level is reported to slowly decrease over a month after transsphenoidal surgery (TSS), thus the surgical results should be evaluated after 3 months. To know the longitudinal shift of blood IGF-1, we conducted retrospective survey of changes in blood IGF-1 over two years, which has been rarely investigated. In addition, we analyzed GH secretory state in the first year which seems to influence the changes in IGF-1 levels.

Methods: 1) Blood IGF-1 levels were measured for longer than 2 years after TSS in 33 patients whose nadir GH during postoperative OGTt was under 1 ng/mL. These changes in IGF-1 levels were assessed by SD (standard deviation) based on standard IGF-1 values of age- and sex-matched Japanese population.

2) Nadir GH during postoperative OGTt was compared between 1-2 weeks after and 3-12 months after the surgery in 35 patients.

Results: 1) Blood IGF-1 gradually declined after three months; 232.4 (mean) ng/ml at 3-12 months, 203.9 ng/ml at 12-24 months, and 200.3 ng/ml at 24-36 months.

2) Their SD values also slowly decreased after three months; 1.74 (mean) at 3-12 months, 1.28 at 12-24 months, and 1.18 at 24-36 months.

3) Nadir GH decreased from 0.83±0.73 ng/ml at 1-2 weeks to 0.68±0.87 ng/ml at 3-12 months.

4) The ratio of patients with nadir GH under 1 ng/mL increased from 71.4% at 1-2 weeks to 80% at 3-12 months.

Conclusion: The slow decrease of the IGF-1 levels continued over the first month, even after the

first year, after TSS. The declination values are greater than those accompanied with aging. This declination may be a reflection of the slow decrease or late normalization of GH secretion.

None of the authors have any relationships to disclose.

Poster #44

SYMPTOMATIC SELLAR ARACHNOID CYSTS TREATED WITH SIMPLE CYST OBLITERATION: IMPACT ON PITUITARY FUNCTION

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Background: Symptomatic sellar arachnoid cysts (AC) are uncommon and have typically been treated via the transsphenoidal route. We evaluate the impact of reinforcing a defective diaphragma and obliterating the cyst cavity with adipose tissue on AC resolution and pituitary hormonal function.

Methods: Retrospective analysis of patients who underwent an endonasal transsphenoidal obliteration of symptomatic AC with fat graft and skull base repair.

Results: Between 01-2001 and 09-2010, 8 patients with a sellar AC were identified (6 females, 2 males, mean age 57 years) who underwent 9 procedures (one recurrence). Clinical presentation included headache (n=4), visual loss (n=4) and endocrinopathy (n=5, 62.5%). Hormonal deficits included hypogonadism (n=4), hypothyroidism (n=3), adrenal insufficiency (n=3), hyperprolactinemia (n=2). Regarding growth hormone (GH) deficiency, one patient presented with isolated GH deficiency and none of the patients with multiple anterior axis dysfunction had low IGF-1 values. However no stimulation test was done pre-operatively. Maximal cyst diameter averaged 22 mm (range 15 to 32 mm). At surgery, the sellar communication to the subarachnoid space was deliberately not enlarged. Postoperatively (6-53 months), endocrinopathy improved in 60% (3/5) with PRL normalizing in two patients and IGF-1 in one. Although there were no new hormonal deficits, none of the 3 patients with multiple anterior axis dysfunction had improvement of these axis post-operatively. Headache improved in 100% (4/4) and vision improved in 100% (4/4). There were no CSF leaks, meningitis or new neurological deficits.

Conclusion: In this small series, sellar ACs were effectively treated by endonasal fenestration and obliteration with a sellar fat graft. This simplified technique which deliberately avoids enlarging communication to the subarachnoid space appears to effectively disrupt cyst progression. Despite the initial compressive effect of the graft within the sella upon the gland, hormonal improvement was seen in 3 patients and no new pituitary hormonal deficits occurred.

None of the authors have any relationships to disclose.

Poster #45

THE ENDOSCOPIC SURGERY IMPROVES THE OUTCOME OF THE TRANSSPHEROIDAL SURGERY IN THE PATIENTS WITH FUNCTIONAL PITUITARY ADENOMAS

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We have introduced the endoscopy system for transsphenoidal adenectomy of functional pituitary adenomas since 2000. We followed-up the surgical results of functional pituitary adenomas between 2000 and 2010. [Patients and methods] We operated on 195 patients who were diagnosed with functional pituitary adenomas from 2000 to 2010. The patients comprised 93 with GHoma, 79 with PRLoma, 16 with ACTHoma and 9 with TSHoma (including 2 patients with both TSH and GH production tumors). The postoperative remission rate and pituitary function preservation in these patients were examined. [Results] Sixty of 93 patients (65%) with GHoma recovered to remission criteria after transsphenoidal surgery with endoscopy. The serum PRL concentrations decreased to less than 10 ng/ml in 66 of 79 patients (84%) with PRLoma on postoperative day 1. The serum PRL concentrations were less than 5 ng/ml in 47 of 79 patients (59%) on postoperative day 1. In 12 of 16 patients (71%) with ACTHoma, the serum cortisol concentrations were less than 2µg/dl after surgery or when examined with the dexamethasone suppression test. In all patients with TSHoma, their serum TSH concentrations were less than 0.4 mIU/ml. In patients with GHoma or PRLoma, the post-surgical remission rate improved slightly compared with that using microscopy alone. [Conclusion] Detailed observations were rendered possible using endoscopy, and the postoperative remission rate and preservation of pituitary functions in patients with functional pituitary adenomas were established with useful quality-of-life (QOL) improvement. The endoscopy system is less invasiveness and improves the outcome of transsphenoidal surgery.

None of the authors have any relationships to disclose.

Poster #46

THE VALUE OF THE ENDOSCOPE IN MICROSCOPIC ENDONASAL PITUITARY ADENOMA SURGERY: A MUST FOR EVERY CASE

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Introduction: While the microscopic approach for pituitary adenoma removal constitutes the “gold standard”, endoscopy as a visual aid (endoscope-assisted) or as the sole visual method (fully endoscopic) is increasingly utilized. Herein we assess the value of endoscopy for finding additional tumor in microscopic pituitary surgery.

Methods: All consecutive patients who underwent endoscope-assisted microsurgical removal of pituitary adenoma were included and retrospectively reviewed. The utility of the endoscope (0, 30 and/or 45 degrees) for finding and removing additional adenoma not visualized by the microscope was determined by review of operative reports. After maximal tumor removal under microscopic visualization, cases were categorized as to whether endoscopy confirmed completeness of removal or if additional tumor was seen and removed.

Results: Between July 2007–December 2010, 166 consecutive patients (51% women, mean age 49 years) underwent 175 endoscope-assisted adenoma removals including 41 endocrine-active microadenomas and 134 macroadenomas (50 endocrine-active); 22% had prior surgery. After microscopic removal, endoscopy revealed residual tumor in 41% (71/175) of cases. Of these, additional tumor was removed in 61 (86%) based on endoscopic visualization, including 40% (53/134) of macroadenomas and 20% (8/41) of microadenomas. Residual tumor blind to the microscope was typically in the suprasellar extension and folds of the collapsed diaphragma or along the medial cavernous sinus wall. Overall, 85% of endocrine inactive tumors achieved gross total removal and 67% of endocrine-active adenomas achieved early remission.

Conclusion: The endoscope revealed residual adenoma in 41% of cases after microscopic removal; additional tumor was removed in 86% of these cases. While longer follow-up is needed, it appears the panoramic visualization and magnification of the endoscope facilitates more complete tumor removal and will likely translate into higher biochemical remission rates for endocrine-active adenomas. All pituitary surgery for both microadenomas and macroadenomas should be performed with endoscopic-assistance or as a fully endoscopic procedure.

*Daniel F. Kelly is a consultant for Mizuho-America Inc.
None of the other authors have any relationships to disclose.*

Poster #47

TSH-SECRETING ADENOMAS: A SINGLE CENTER EXPERIENCE

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Introduction: TSH-secreting pituitary adenomas are extremely rare. **Aim:** Retrospective analysis of all cases diagnosed at our Neuroendocrine Unit since 1988. **Results:** We have diagnosed, treated and followed 7 patients (4 men) with TSHoma (age: 19–45 y; mean follow up: 8y). Initial complaints were visual impairment, headache, acromegalic features and amenorrhea-galactorrhea, but symptoms and/or signs of thyrotoxicosis were always present and goiter was found in 6 patients. Prior to diagnosis, 2 patients had been treated with anti-thyroid drugs and one with thyroidectomy/131I therapy. Diagnosis was strongly suggested by high FT4 with either normal or high TSH. Alpha-subunit levels were always high. Pituitary scans revealed adenoma (macro-6/micro-1). Co-secretion was observed in 4 cases: PRL, GH and PRL, and GH. Before surgery, somatostatin analogs normalized FT4 levels in 3/4 patients. Six patients were operated; one was cured after pituitary apoplexy. After surgery, 2 patients became euthyroid, 3 remained uncontrolled and post-surgical evaluation is pending in one. Among the 3 patients not controlled by surgery, two received pituitary irradiation: one died due to complications and the other one is on levothyroxine replacement with normal FT4 and high TSH levels, but no tumor growth in 22 y. The third one received 131I, has been on levothyroxine and long-acting somatostatin analog with slightly increased TSH and IGF-I levels but no tumor growth in 12 y. In one patient achieving euthyroidism after surgery, cabergoline was successful in controlling hyperprolactinemia and decreasing tumor remnant. **Conclusions:** Although TSHomas are extremely heterogeneous in clinical presentation, they can usually be diagnosed by routine measurements of serum TSH and FT4 and pituitary MR scans. Long-term control of tumor growth and hyperthyroidism in patients with TSHomas can be variably achieved by isolated or combined therapeutic interventions including somatostatin analogs, pituitary surgery, pituitary radiotherapy and even surgical/radioiodine thyroid ablation in selected cases.

None of the authors have any relationships to disclose.





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