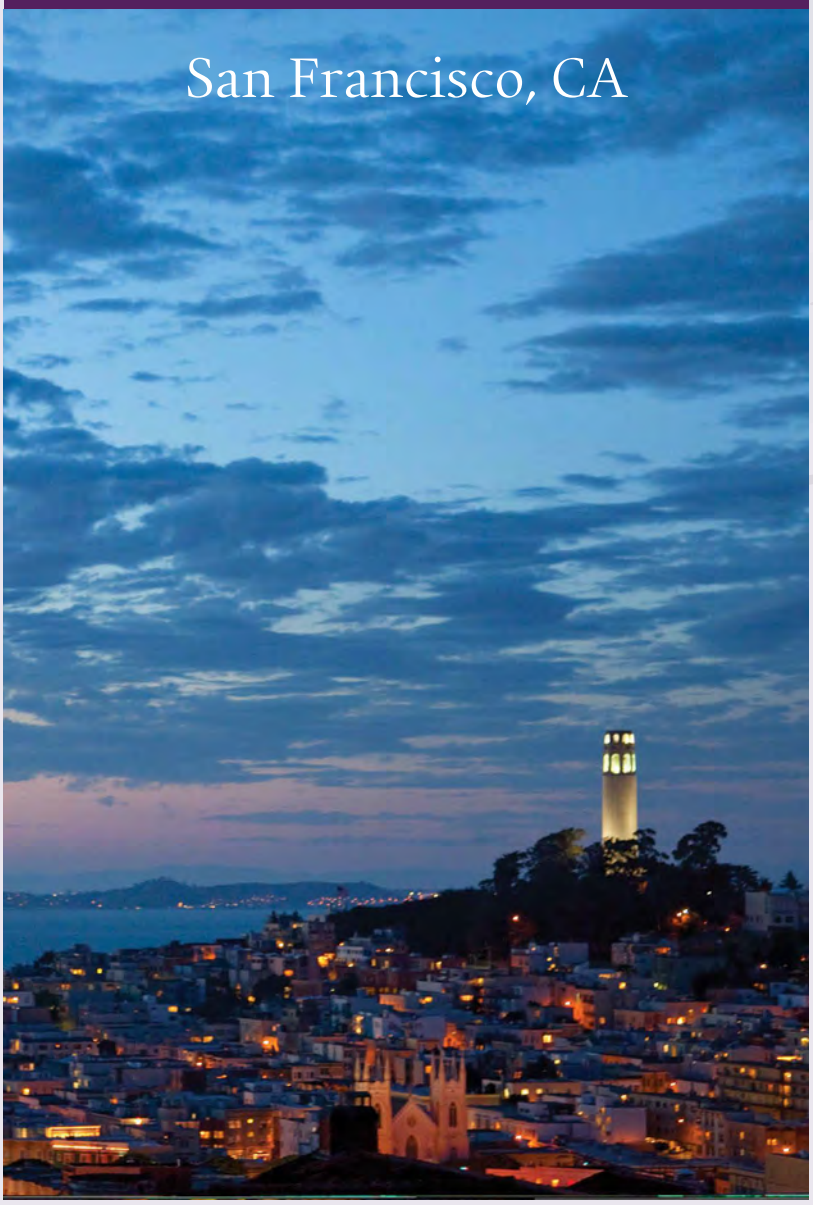
THE PITUITARY SOCIETY
presents the

13th THIRTEENTH INTERNATIONAL PITUITARY CONGRESS

JUNE 12 - 14, 2013

San Francisco, CA



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PROGRAM AND ABSTRACTS

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Welcome

The 13th International Pituitary Congress will provide an exciting forum for member and guest international experts to discuss 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!

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Symposium Schedule

WEDNESDAY, JUNE 12

1:00 pm	Registration - **Grand Ballroom Lobby**	
7:00	OPENING PLENARY LECTURE - **Grand Ballroom**	*Chair: Marcello Bronstein*
	HMGA as a Driver of Pituitary Tumorigenesis	*Alfredo Fusco*
8:00	Welcome Dinner Reception - **Pavilion, Loggia & Roof Garden**	

THURSDAY, JUNE 13

7:00 am	Continental Breakfast - **Terrace & Vanderbilt Rooms**	
I. TUMORS RESISTANT TO MEDICAL TREATMENT - Grand Ballroom		*Chair: Márta Korbonits*
8:00	Mechanisms Underlying Treatment Resistance	*William Farrell*
8:30	Mechanisms for Somatostatin Analog Resistance - Clinical Aspects	*Jens Bollerslev*
9:00	AIP and Somatostatin Analog Resistance	*Mônica Gadelha*
9:30	Wnt/beta–catenin Signaling in Craniopharyngioma	*Mehul Dattani*
10:00	Coffee Break & Poster Session -**Terrace & Vanderbilt Rooms**	
II. NEW INSIGHTS IN PITUITARY BIOLOGY - Grand Ballroom		*Chairs: Ariel Barkan and Anna Spada*
10:30	Mechanisms for Pituitary Cell Fate Choice	*Jacques Drouin*
11:00	Transgenic Prolactin Cancer Models	*Nelson Horseman*
11:30	GH/IGF-I and Cancer	*Michael Waters*
12:00 Noon	Immunomodulation and Hypophysitis	*Patrizio Caturegli*
12:30 pm	Recombinant Human TSH - 20 Years of Experience in Man	*Richard Robbins*
III. MEET THE PROFESSOR CONCURRENT LUNCH WORKSHOPS - SESSION I		
1:00 - 1:45	Craniopharyngioma - Management Challenges - **Gold Room**	*John Wass*
	Cushing Diagnosis - New Options - **Grand Ballroom**	*Hershel Raff*
	Dopamine Agonist Withdrawal - When and How - **Venetian Room**	*Janet Schlechte*
	Metabolic and Bone Benefits of Adult GH Replacement - **Pavilion Room**	*Ken Ho and Nicholas Tritos*
	Traumatic Brain Injury and Hypopituitarism - **French Room**	*Christopher Thompson*
IV. MEET THE PROFESSOR CONCURRENT LUNCH WORKSHOPS - SESSION II		
1:45 - 2:30	Craniopharyngioma - Management Challenges - **Gold Room**	*John Wass*
	Cushing Diagnosis - New Options - **Grand Ballroom**	*Hershel Raff*
	Dopamine Agonist Withdrawal - When and How - **Venetian Room**	*Janet Schlechte*
	Metabolic and Bone Benefits of Adult GH Replacement - **Pavilion Room**	*Ken Ho and Nicholas Tritos*
	Traumatic Brain Injury and Hypopituitarism - **French Room**	*Christopher Thompson*
2:30	Coffee Break & Poster Session - **Terrace & Vanderbilt Rooms**	

Symposium Schedule

V. CUSHING DISEASE - Grand Ballroom		*Chair: Stephan Petersenn*
3:00	How to Differentiate Central from Ectopic ACTH-Dependent Cushing's Syndrome	*John Newell-Price*
3:30	Peri-operative Management of Patients with Cushing's Disease	*Ashley Grossman*
4:00	Pregnancy and Cushing's Syndrome: A Preliminary Report	*Susan Webb*
4:30-5:30	Poster Session - Terrace & Vanderbilt Rooms	
	Gala Dinner	
6:30	Cocktail Reception - Venetian Room	
7:30	Gala Dinner - Grand Ballroom	

FRIDAY, JUNE 14

8:00 am	Continental Breakfast - Terrace & Vanderbilt Rooms	
VI. AGGRESSIVE PITUITARY TUMORS - Grand Ballroom		*Chair: Luis Syro*
8:45	Aggressive Pituitary Adenomas	*Kalman Kovacs*
9:15	Aggressive Pituitary Tumors: Clinical Markers	*Niki Karavitaki*
9:45	MRI and Surgery in Aggressive Pituitary Adenomas	*Engelbert Knosp*
VII. HOT TOPICS - Grand Ballroom		*Chairs: Paolo Beck-Peccoz and Felipe Casanueva*
10:15	STAT3 Induces Growth Hormone Expression in Pituitary Somatotroph Cells	*Cuiqi Zhou*
10:30	Completely Humanizing Prolactin Rescues Infertility in Prolactin Knockout Mice	*Karen Gregerson*
10:45	Temozolomide and Aggressive Pituitary Tumours: Longer-term Follow-up	*Ann McCormack*
11:00	Novel and Highly Sensitive EIAs for the Differential Diagnosis (DDx) Between Cushing's Disease (CD) and Ectopic ACTH Syndrome (EAS)	*Hideki Katakami*
11:15	Coffee Break - Grand Ballroom Lobby	
VIII. DEBATES - Grand Ballroom		
11:30	Cushing Treatment	*Moderator: Jérôme Bertherat* *Marco Boscaro* *Maria Fleseriu* *Brooke Swearingen*
12:00 pm	Acromegaly Treatment	*Moderator: Christian Strasburger* *John Ayuk* *Philippe Chanson* *Vivien Bonert*
12:30-1:30	Presidential Address & Awards Luncheon - Gold Room	*Mark Molitch*

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ABSTRACTS
INVITED LECTURES

OPENING PLENARY SESSION

Chair: Marcello Bronstein
Disclosure: Marcello Bronstein has no relationships to disclose.

HMGA as a Driver of Pituitary Tumorigenesis

Alfredo Fusco

Istituto di Endocrinologia ed Oncologia Sperimentale del CNR c/o Dipartimento di Biologia e Patologia Cellulare e Molecolare Istituto di Endocrinologia ed Oncologia Sperimentale del CNR, Naples, Italy

The High Mobility Group A (HMGAs) protein family consists of four members, HMGA1a, HMGA1b and HMGA1c (encoded through alternative splicing by the HMGA1 gene) and HMGA2 (encoded by the HMGA2 gene). The HMGA proteins interacting with the transcriptional machinery can regulate, positively or negatively, the expression of several genes. HMGA protein expression is abundant during embryogenesis whereas it is absent or detected at very low levels in normal adult tissue. Conversely, HMGA overexpression is a constant feature of human malignant neoplasms.

Transgenic mice overexpressing Hmga1 or Hmga2 genes develop mixed GH/PRL-secreting pituitary adenomas, and HMGA2 gene is amplified and overexpressed in several pituitary adenomas. The overexpression of the HMGA genes would induce pituitary adenomas by enhancing the activity of the transcription factor E2F1, by upregulating the expression of cyclin B2 and, likely, other genes mainly involved in the regulation of the cell cycle.

We have recently analyzed the miRNA expression profile of pituitary growth hormone (GH)–adenomas that correspond to about 20% of all pituitary adenomas. We have identified a set of miRNAs, including miR-34b, miR-326, miR-432, miR-548c-3p, miR-570 and miR-603, drastically and constantly downregulated in GH adenomas and in other types of adenoma. These miRNAs target genes such as HMGA1, HMGA2 and E2F1, whose overexpression and/or activation plays a critical role in pituitary tumorigenesis. The overexpression of these downregulated miRNAs has a negative role on the regulation of cell growth by inhibiting the G1-S transition of the cell cycle that is controlled by the HMGA proteins upregulating the expression of the E2F1-dependent genes. Finally, an inverse correlation was found between the expression of these miRNAs and HMGA1 and HMGA2 protein levels in GH adenomas.

Therefore, the downregulation of these miRNAs may represent an important event in the development of human pituitary adenomas by leading to an upregulation of the HMGA protein levels.

Disclosure: Alfredo Fusco has no relationships to disclose.

TUMORS RESISTANT TO MEDICAL TREATMENT

Chair: Márta Korbonits

Disclosure: Márta Korbonits has no relationships to disclose.

Mechanisms Underlying Treatment Resistance

William E. Farrell

ISTM, University of Keele, UK

The identification of effective drug therapies that supress inappropriate hormone secretion and inhibit pituitary tumour growth present significant challenges. Nonetheless, these dual pharmacologic outcomes are achieved for most but not all prolactinoma through use of therapeutics that engage the dopamine receptor (D2R), or use of chimaeras that co-engage the somatostatin receptor (SSTR). However, these and other drug based approaches directed toward GH and ACTH secreting adenomas achieve benefit in a significantly smaller proportion of cases. More recent approaches have focused on retinoic acid (RA), initially shown to prevent experimental Cushing syndrome and where subsequent studies showed that the inhibitory effects were mediated, at least in part, through induction of BMP-4. In those cases where resistance to medical interventions are encountered it is frequently, but not invariantly, attributed to the absence or reduced expression of analogue specific receptor(s).

In recent studies we showed that reduced expression of the D2R receptor in the GH3 pituitary cell line was through epigenetic silencing. Incubation of these cells with the epidrugs, zebularine and TSA restored receptor expression and an augmented apoptotic response to dopamine analogue challenges. Moreover, primary prolactinomas that were resistant to pharmacological intervention showed reduced expression of the D2R and these too harboured histone modifications associated with gene silencing. For BMP-4 increased and decreased expression of this cytokine has been reported in prolactinoma and corticotroph adenomas respectively our own studies confirmed these findings and showed reduced BMP-4 expression in the majority of pituitary adenoma subtypes with the exception of prolactinomas. In primary tumours and pituitary cell lines reduced expression of BMP-4 is associated with epigenetic changes. Epidrug challenges reversed these changes and led to re-expression of BMP-4 in cell lines.

The bifunctional role of BMP-4 as a growth promoting and growth inhibiting protein in prolactinoma and in corticotroph cell respectively was investigated though RA challenge of pituitary cell lines. RA induced expression of BMP-4 was only apparent in cells pre-incubated with epidrugs. A bi-functional role for BMP-4 was reinforced where RA induced expression in epidrug incubated cells led to increase or decrease in cell number and CFE in GH3 and AtT-20 cells respectively. These studies show the potential of combined drug challenges as a treatment option, where epidrug renders silenced genes responsive to conventional therapeutic options.

Disclosure: William Farrell has no relationships to disclose.

Mechanisms for Somatostatin Analog Resistance – Clinical Aspects

Jens Bollerslev

Section of Specialized Endocrinology, Oslo University Hospital, Oslo, Norway

Somatostatin Analog (SA)'s have become the cornerstone of medical treatment for acromegaly, especially for primary medical therapy. Endogenous somatostatins have a relatively uniform affinity for the five somatostatin receptor (SSTR)'s; the clinically used SA's binds primarily to SSTR2 and to some degree to SSTR5. New analogs exert a more uniform binding, with the highest affinity for SSTR5. As a primary option, SA can control tumor growth in most patients, whereas biochemical control is only obtained in up to 60% of unselected patients.

Tachyphylaksis is not a clinical problem in long-term treatment with SA's, but a few patients do seem to loose their sensitivity related to a down-regulation of SSTR2a. The good responder to SA treatment has a high expression of SSTR2a in the membrane of the somatotroph adenoma. The tumors are histopathologically packed with secretory granules appearing as a densely granulated phenotype corresponding to the clinical MR-finding on a T2 weighted scan showing hypointensity. Tumor cells are well differentiated with an epithelial phenotype. In contrast, the tumors of the poor responders appear with a more mesenchymal phenotype, having fewer if any granules and appearing more hyperintense on the T2 scan. The non-responding tumors are typically larger, more invasive and producing less GH per volume unit. This epithelial to mesenchymal transition in the somatotroph adenoma is related to attenuated E-cadherin expression. A mechanism for this loss of E-cadherin has recently been suggested related to alternative splicing, potentially regulated by *ERSP1*. The truncated form of SSTR5 has also been related to alternative splicing.

In conclusion, epithelial to mesenchymal transition of the somatotroph adenoma seems to be of importance for resistance to SA treatment. Recent studies have given insight into potential mechanisms behind this process and identified *ESRP1* as a regulater of alternative splicing of importance for this transition.

Disclosure: Jens Bollerslev is on the Advisory Board of and is a speaker for Novartis and is a speaker for Pfizer.

AIP and Somatostatin Analog Resistance

Mônica Gadelha

Neuroendocrine Research Center, Endocrinology Unit, Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Somatostatin analogs (SSAs) are the most widely used drugs for the treatment of acromegaly. However, in a considerable number of patients, disease activity cannot be fully controlled with these drugs. Many mechanisms and predictor factors for SSA resistance have been described.

Mutations in the aryl hydrocarbon receptor-interacting protein (AIP) tumor suppressor gene have been identified in approximately 20% of the familial isolated pituitary adenoma (FIPA) families. In addition to FIPA cases, germline AIP mutations may also occur in seemingly sporadic young onset pituitary adenomas (simplex cases). No somatic mutation has been reported in pituitary adenomas to date.

The vast majority of the AIP-mutated FIPA patients and simplex cases present young-onset pituitary adenomas secreting GH, prolactin, or both. AIP-mutated somatotropinomas are usually larger tumors with more aggressive behavior than FIPA cases without AIP mutation or sporadic acromegalic patients and are commonly totally or partially resistant to SSAs.

Interestingly, 50% of sporadic somatotropinomas show low intrinsic AIP protein expression with no AIP mutation. These adenomas have a similar phenotype to that seen in AIP-mutated patients. In addition, it was observed that SSA treatment increases AIP expression and that AIP overexpression increases ZAC1 (zinc finger protein which regulates apoptosis and cell cycle arrest) expression suggesting that AIP may be the link between SSAs and ZAC1.

There is no significant difference in AIP mRNA expression between sporadic somatotropinomas with low or high AIP expression. This suggests that the expression of AIP protein might be regulated post-transcriptionally. We have identified and proved that microRNA (miR)-34a is a negative regulator of AIP protein expression and hypothetised that miR-34a could be responsible for the low AIP expression observed in half of the sporadic somatotropinomas.

In conclusion, low AIP expression found in FIPA and in sporadic acromegalic patients, the former due to germline mutations and the latter due to miR regulation, may be involved in the molecular basis of SSAs resistance, as AIP expression seems to be involved in the mechanism of action of this class of drugs.

Disclosure: Mônica Gadelha is a speaker for, is an Advisory Board Member, and receives research support from Novartis, and is a speaker for Ipsen.

Wnt/beta-catenin Signaling in Craniopharyngioma

C Gaston-Massuet, C Andoniadou, JP Martinez-Barbera, MT Dattani

UCL Institute of Child Health, London, UK

Canonical Wnt/beta-catenin signalling plays an essential role during normal development and adulthood but when deregulated can cause disease, including cancer. We have shown that genetic expression of a degradation-resistant mutant form of beta-catenin in early Rathke's pouch (RP) progenitors leads to pituitary hyperplasia and severe disruption of the Pit1-lineage differentiation resulting in extreme growth retardation and hypopituitarism. These mutant mice mostly die perinatally, but those that survive weaning develop lethal pituitary tumors, which closely resemble human adamantinomatous craniopharyngioma (ACP), a benign epithelial tumor that is associated with mutations in the beta-catenin gene *(CTNNB1).* The tumorigenic effect of mutant beta-catenin is only observed when expressed in undifferentiated RP progenitors, but when committed or differentiated cells are targeted to express this protein, tumors do not develop. As observed in human ACP, nucleocytoplasmic accumulation of β-catenin (β-cat^{nc}) and overactivation of the Wnt/ β-catenin pathway occurs only in a very small proportion of cells, which form clusters. Isolation of these cells from tumorigenic mouse pituitaries revealed that they are enriched for colony-forming cells when cultured in stem-cell promoting media, and have longer telomeres, properties that are shared with normal pituitary progenitors/stem cells (PSCs). Additionally, these β-cat^{nc} cells express high levels of secreted mitogenic signals, such as members of the SHH, BMP and FGF family, as well as chemokines and their receptors, thereby suggesting an autocrine/paracrine role of these cells in the pathogenesis of ACP. These pathways are also upregulated in the β-cat^{nc} cell clusters identified in human ACP, suggesting that pituitary stem cells may be implicated in the etiology of human ACP. Our findings demonstrate, for the first time, a causative role of mutated beta-catenin in an undifferentiated RP progenitor in the genesis of murine and human craniopharyngioma. The creation of a mouse model of human ACP will also allow the testing of novel pharmacological targets for the treatment of these devastating childhood tumors.

Disclosure: The authors have no relationships to disclose.

NEW INSIGHTS IN PITUITARY BIOLOGY

Chairs: Ariel Barkan and Anna Spada

Disclosure: Ariel Barkan is an investigator on Novartis protocols, and Anna Spada has no relationships to disclose.

Mechanisms for Pituitary Cell Fate Choice

Jacques Drouin

Institut de Recherches Cliniques de Montréal, QC, Canada

During development, endocrine cells of the pituitary differentiate sequentially from a pool of common progenitors that originate from the oral ectoderm. Until recently, cell fate choices that direct this sequential differentiation scheme had been ascribed to transcription factors (TF) with cell-restricted expression. Hence, the POUhomeo factor Pit1 has a critical role for differentiation of the thyrotrope, somatotrope and lactotrope lineages whereas the Tbox factor Tpit is essential for terminal differentiation of the two POMC-expressing lineages, the corticotropes and melanotropes, and the gonadotropes require the orphan nuclear receptor SF1 for terminal differentiation. Of these lineages, the melanotropes of the intermediate lobe (IL) define a unique tissue, the IL, that is sandwiched between the infundibulum (future posterior lobe) and the anterior lobe. A large body of evidence has identified extensive signaling between neural tissues of the infundibulum and ectodermal derivatives of Rathke's pouch, and the IL is the primary site of these interactions.

Having obtained expression profiles to identify TFs specifically expressed in the IL and melanotropes, we discovered that Pax7 is uniquely expressed in this tissue and cells. Further, we found that Pax7 exerts a Selector gene action on the IL such as it`s epigenetic action on cells of this tissue alters the targets of Tpit-driven differentiation. Pax7 thus exerts a pioneer transcription factor action that remodels the genome for Tpit-dependent differentiation. The outcome of this pioneering action is to activate the melanotrope gene expression program while repressing the corticotrope program. Interestingly, the DNA sequences of Pax7 binding sites involved in pioneering differ from those where Pax7 exerts a traditional TF action.

It is noteworthy that a role for Pax7 appears to be maintained even in species like humans, where a distinct IL is not maintained in the adult. Indeed, Pax7 marks cells of IL origin and thus differentiate corticotrope adenomas of different origins. Pax7-expressing adenomas have been identified both in humans and dogs. The broader importance of genome remodeling for pituitary cell differentiation, development, pathogenesis and possibly therapeutics remains to be explored.

Disclosure: Jacques Drouin has no relationships to disclose.

Transgenic Prolactin Cancer Models

Nelson D. Horseman and Karen A. Gregerson

University of Cincinnati, Cincinnati, Ohio, USA

Prolactin's potential involvement in cancers has been the subject of intense scrutiny and conflict for decades. In rodents the situation is simple: continuous exposure to high levels of PRL clearly causes breast cancers, which resolve when PRL is withdrawn. In humans, it seems nothing is so simple. Not only does hyperprolactinemia not routinely cause breast cancers, inhibiting PRL has never been shown to be curative. The kind of incisive experimental work necessary to resolve this obvious contradiction could never be done in humans or primate models, so genetically modified rodent models remain our best hope. In this talk we will review three productive areas of research that may illuminate the possible relationship of human breast cancer with PRL. First, RANK-ligand, a local cytokine, is a powerful breast cell mitogen that is normally tightly controlled by progesterone and PRL. In some cancers RANKL may become PRL-independent, rendering them susceptible to uncontrolled proliferation. A second local tumor progression factor is PTHrP, which is indirectly controlled by PRL in normal breast cells. The normal regulation of PTHrP by PRL may be lost in cancer cells due to selection for altered serotonin signaling. Thirdly, a new transgenic model in which human PRL is expressed under the control of human promoters may resolve whether autocrine-paracrine secretion of PRL by breast cells can promote cancer. This new model also sheds light on the etiology of benign pituitary adenomas.

Disclosure: The authors have no relationships to disclose.

GH/IGF1 and Cancer

MJ Waters

Institute for Molecular Bioscience, University of Queensland, Australia

Despite the lack of evidence that GH replacement at normal doses in the clinic promotes primary cancers, there is substantial concern that GH/IGF1 may be acting to promote tumour growth. This concern stems from several different sources. First, acromegalics do have an increased risk of colon cancer and thyroid cancer, and possibly other forms of cancer. Second, humans lacking functional GH receptor are protected from cancer deaths. Third, epidemiologic studies link increased height, IGF1 level and breast cancer incidence. Fourth, the signalling pathways activated by GH and by IGF1 are those used in tumour promotion (ERK, Akt, Src, STAT3, STAT5 etc). It is notable that these pathways are also recruited by the prolactin receptor, which is also activated by hGH, and associated with some epithelial cancers. Fifth, numerous animal studies link absence of GH or GH receptor with resistance to tumour growth. Finally, there is now good evidence in humans and dogs that autocrine GH and prolactin expression are associated with tumour progression, as is increased expression of their receptors.

In order to rationalize these findings we should remember that cells protect themselves against excess GH action through negative regulation (receptor downregulation, desensitization via phosphatases, and SOCS), and these evidently keep the tumorigenic actions of GH and prolactin in check. Apparently autocrine GH action is not so susceptible to these regulators, and potential reasons for this will be proposed. We should also consider that our measure of safety of GH replacement is based on a comparison with tumour incidence in normal individuals who, according to the findings with individuals harbouring GH receptor mutantion, themselves have a finite tumour incidence as result of normal GH/IGF1 action.

Reference: Chhabra Y, Waters MJ, Brooks AJ (2011) Role of the GH-IGF1 axis in cancer. Expert Review of Endocrinology & Metabolism 6, 71-84. Access via Google Scholar.

Disclosure: MJ Waters has no relationships to disclose.

Immunomodulation and Lymphocytic Hypophysitis

Patrizio Caturegli

The Johns Hopkins University, Department of Pathology, Baltimore, Maryland, USA

Autoimmune hypophysitis is a chronic inflammation of the pituitary gland that is receiving greater attention from endocrinologists and oncologists alike. It was considered a rarity and largely ignored by the medical community until a few years ago when it was reported at unexpectedly high frequency in cancer patients undergoing immunotherapy. Hypophysitis can then be classified into primary and secondary.

Primary hypophysitis includes the forms where the cause and mechanism of the disease remain unknown. It was first reported in 1962 and in approximately 800 published patients thereafter. Pathologically is mainly characterized by a lymphocytic infiltration of the pituitary gland, although granulomatous, xanthomatous, IgG4 plasmacytic, and necrotizing forms are also described. Despite the rarity, primary hypophysitis is clinically significant because it enters in the differential diagnosis of about 30 other diseases that manifest as a non-hormone secreting sellar mass, which typically require a very different treatment.

Secondary hypophysitis includes the forms where an initiating agent or mechanism is identifiable. Among them, hypophysitis caused by antibodies that block cytotoxic T lymphocyte antigen 4 (CTLA-4) are the most common. CTLA-4 is a molecule expressed mainly on T lymphocytes that, when engaged by the cognate receptor, induces inhibitory signals that suppress T cell activation. When CTLA-4 is blocked, T cells remain active. This feature is being exploited to boost the response of the immune system against cancer cells. CTLA-4 can be blocked with monoclonal antibodies. Of them, ipilimumab (Yervoy, made by Bristol Myers Squibb) is the most widely used and approved by FDA in March 2011 for the treatment of advanced melanoma. Ipilimumab is now been used in several other types of cancers, including prostate, pancreatic, and non-small cell lung cancers. The treatment is expensive (4 injections cost $120,000) and associated with numerous side effects called immune-related adverse events (irAEs). The most common irAEs are dermatitis, colitis, hypophysitis and hepatitis. irAEs often correlate with anti-tumor response (but not always), and have an orderly sequence of appearance: dermatitis (rush and pruritus) develops first, followed by colitis, and finally by liver toxicity and hypophysitis. Hypophysitis secondary to ipilimumab can be difficult to recognize (sometimes patients end up in the emergency room) and is not as well responsive to glucocorticoid treatment and ipilimumab withdrawal as other irAEs are

There have been 18 published clinical trials from 2003 to present that have used ipilimumab and have reported hypophysitis as an irAE. The mean incidence of hypophysitis is about 3% (54 out of 1867 total patients). It remains unknown why hypophysitis, traditionally considered a rare autoimmune disease, is seen with surprisingly high incidence during ipilimumab treatment.

At this congress I will present our mouse and human studies focused on improving the diagnosis and understanding the pathogenesis of hypophysitis secondary to CTLA-4 blockade.

Disclosure: Patrizio Caturegli has no relationships to disclose.

Recombinant Human TSH – 20 Years of Experience in Man

Richard J. Robbins

Endocrinology Division, Department of Medicine, The Methodist Hospital, Houston, Texas, USA

TSH was first extracted from bovine pituitary glands, for sale, in 1945. It was used to stimulate radioiodine uptake in thyroid cancer patients in the late 1940s, however allergic reactions and autoantibodies led to cessation of its use. In the late 1980s, two translational research groups led by Bruce Weintraub and Ione Kourides isolated sequences of the human thyrotropin beta subunit gene. This was followed by production of fully intact and active human recombinant TSH in human embryonic kidney cells by Wondisford and Weintraub. Collaboration between the Genzyme Company and several academic groups resulted in large-scale production of highly purified and active human recombinant TSH in Chinese Hamster Ovary cells. This product, designated Thyrogen®, was tested in vitro, in animals, and in Phase I, II, and III human studies and was found to be safe, effective, and without allergic reactions or neutralizing antibody production. It was initially approved by the FDA, in December 1998, for use in detecting residual thyroid cancer based on a rise in serum thyroglobulin and uptake of radioiodine on whole body scanning. It was subsequently used to help achieve radioiodine remnant ablation without the need to make the patients hypothyroid. Many investigators showed that rhTSH preparation while euthyroid was as effective as hypothyroid preparation, at achieving remnant ablation. Furthermore, the short- and long-term cancer recurrence rates were also found to be comparable to the hypothyroid preparation method. The FDA approved the remnant ablation indication in December 2007. Thyrogen® was also shown to be helpful for patients who could not make endogenous TSH or were too ill to sustain 4-6 weeks of hypothyroidism. Most recently, Thyrogen® has been shown to be equally effective as hypothyroidism as preparation for the treatment of metastatic well-differentiated thyroid cancer; although this last use is not approved by the FDA. Lastly, Thyrogen® has been shown to be a useful adjuvant in radioiodine treatment of large benign goiters where it stimulates significantly greater goiter shrinkage than radioiodine alone. This story is a great example of translational research in which sequencing of short stretches of DNA ultimately led to important and effective treatments for patients with thyroid neoplasia.

Disclosure: Richard Robbins has no relationships to disclose. The presentation will include discussion of product(s) unlabeled (off-label) for use as approved by the FDA or by the equivalent regulatory authority in the country in which the studies or trials were performed.

MEET THE PROFESSOR CONCURRENT WORKSHOPS

Dopamine Agonist Withdrawal - When and How

Janet A. Schlechte

University of Iowa, Iowa City, Iowa, USA

Despite the efficacy and widespread use of dopamine agonists in treatment of prolactinomas, how long to treat, the effects of drug withdrawal and the safety of long term therapy remain important challenges. A number of studies have shown that the majority of patients develop recurrent hyperprolactinemia after withdrawal of cabergoline or bromocriptine therapy. Most recurrences occur within the first year after therapy is withdrawn, and the level of prolactin and tumor size at the time of drug withdrawal are the major predictors of recurrence.

The precise duration of therapy prior to attempting withdrawal has not been established. Recent guidelines suggest a taper and discontinuation after 2 years of therapy if the prolactin is normal and the tumor is absent or reduced in size. Tumor enlargement is not a prominent feature of recurrent hyperprolactinemia but is more likely to occur in those with a post treatment tumor remnant. About 1/3 of patients develop hypogonadism after drug withdrawal.

A slow drug taper is not necessary in patients with a microadenoma. For patients with a macroadenoma the drug should be tapered slowly with careful monitoring of serum prolactin levels every 3 months. If there is a marked elevation in prolactin or onset of symptoms suggestive of tumor growth an MRI should be obtained. With hypogonadism, estrogen or testosterone can be useful, but sex steroids should be used with caution in patients with macroadenomas.

Use caution in attempting drug withdrawal in treatment of prolactinomas as followup studies are short and published findings relate to carefully selected patients.

Disclosure: Janet Schlechte has no relationships to disclose.

Cushing Diagnosis – New Options

Hershel Raff

Endocrine Research Laboratory, Aurora St. Luke's Medical Center, Aurora Research Foundation, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

Late-night salivary cortisol (LNSC) measurement is now established as a sensitive and specific diagnostic test for the diagnosis of Cushing's syndrome. However, it has been slow to be universally accepted and adopted, particularly in routine clinical practice and in all reference laboratories around the world. Furthermore, with increased utilization and new assay methods, significant new issues and caveats have arisen. This Meet the Professor session will discuss (a) issues arising from new assay methodologies, (b) the optimal number of LNSCs to be measured, (c) the problem of salivary sample contamination, (d) the use of LNSCs in screening patients with adrenal incidentalomas, and (e) surveillance of patients for remission/recurrence after pituitary surgery. Immunoassay of salivary cortisol performs as well, if not better, than liquid chromatography/tandem mass spectrometry (LC-TMS), except for the issue of contamination of saliva samples with widely available and over-the-counter hydrocortisone (cortisol) topical ointments. Samples with remarkably high LNSC out of proportion to the clinical scenario should be evaluated for cortisone by LC-TMS; a very high cortisol:cortisone ratio indicates contamination of saliva with cortisol. It is recommended that at least two LNSCs be performed 1-2 days apart. The low-dose overnight dexamethasone suppression test seems to perform better than LNSC for evaluating adrenal incidentalomas. Finally, LNSC is an excellent tool for following patients after pituitary surgery for Cushing's disease. The increased use around the world of LNSC for the diagnosis of endogenous Cushing's syndrome should continue to improve the detection of this enigmatic disorder and also improve our understanding of its incidence in the general population and its epidemiology.

Disclosure: Hershel Raff has no relationships to disclose.

Craniopharyngioma - Management Challenges

John A. H. Wass

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

Craniopharyngioma still significantly interferes with the quality and quantity of life. While the pathogenesis of adenomatous craniopharyngioma is known in 70%, that of papillary craniopharyngioma remains completely unknown.

These tumours, 50% of which occur in childhood, have an incidence of 1.3 per million/person/year. Surgery more often than previously can be accomplished by the transsphenoidal route but with large suprasellar extensions is more frequently dealt with using a pterional craniotomy. If surgery cannot be successful rather than an aggressive approach, which may cause hypothalamic damage, survival is similar after partial removal and post operative radiotherapy.

Morbidity remains a considerable problem, hypopituitarism is frequent and hypothalamic complications remain a problem. Most devastatingly obesity is present in approximately 50% of children treated, likely caused by destruction of the ventromedial hypothalamus. Other aspects of hypothalamic damage include adipsic diabetes insipidus, which can also be very challenging to manage.

Mortality remains highest in this pituitary or para-pituitary lesion and management is optimal with multidisciplinary input from endocrinologists, neurosurgeons, radiotherapists, oncologists and pathologists.

Basic research on the aetiology needs further work particularly in papillary craniopharyngioma and the optimal outcome of recurrent craniopharyngiomas, be it with intracystic irradiation or other means requires more studies in order to clearly delineate what treatment is optimal in these circumstances.

Further reading:

Pituitary 2013, vol 16 (1); 1-56 Special section on Craniopharyngiomas, Eds Niki Karavitaki and John Wass

Endocr Rev. 2006 Jun;27(4):371-97. Craniopharyngiomas Karavitaki et al

Disclosure: John Wass has no relationships to disclose.

The Promise of Growth Hormone: Separating Fact From Fiction

Ken Ho

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

GH regulates lipid, protein and carbohydrate metabolism in the adult after the cessation of linear growth. GH deficiency in adults increases body fat mass, reduces lean mass, bone mass, organ size, strength and fitness, changes mimicking those of senescence. GH replacement normalises body composition, muscle strength, physical fitness in patients with organic GH deficiency. Thus GH is a powerful metabolic hormone controlling body composition and function

GH is produced throughout adult life but its secretion falls with increasing age. There is speculation that diminishing output of GH causes loss of muscle and bone mass and an a gain of fat mass with advancing years. This has led to claims that GH can be used as an anti-aging hormone to improve quality of life and longevity.

GH supplementation to the elderly reduces fat mass, increases lean mass, but does not improve physical or cognitive function. Frequent adverse effects including arthrlalgia, hyperinsulinaemia and hyperglycaemia are observed. There is emerging epidemiological evidence linking insulin and IGF-I status to increased cancer risk. In animals, longevity is prolonged rather than shortened in GH deficiency.

The value of GH supplementation in the elderly remains to be established in contrast to clear benefits of replacement in organic GH deficiency. The epidemiological link between IGF-I and the negative impact of GH on longevity in animals, call for caution in the use of GH in the elderly.

Disclosure: Ken Ho has no relationships to disclose.

Metabolic and Bone Benefits of Adult GH Replacement

Nicholas A Tritos

Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Clinical significance:

In adults, growth hormone deficiency (GHD) can be a consequence of organic hypothalamic pituitary disease (as a result of space occupying lesions, trauma, surgery, radiation therapy or subarachnoid hemorrhage) occurring throughout the lifespan (1). Congenital hypopituitarism caused by genetic or structural etiologies may involve lifelong GHD. In addition, idiopathic GHD of childhood onset may persist in adulthood.

Adult GHD is associated with increased visceral adiposity, decreased fat free mass and several adverse cardiometabolic risk factors (1-3). In addition, adult GHD is associated with decreased bone mineral density (BMD) as well as an increased fracture risk (4, 5).

Growth hormone replacement increases fat free mass and bone mineral density, decreases visceral adiposity, and improves lipid profile and C reactive protein (CRP) levels (1). There can be variable effects on glucose homeostasis. A review of the effects of GH replacement on quality of life is beyond the scope of this presentation (6).

Learning objectives:

1. Discuss the effects of GH replacement on BMD in adults.

2. Review metabolic effects of GH replacement, including effects on lipids and glucose homeostasis in adults.

3. Describe the effects of GH replacement in young adults with GH deficiency of childhood onset persisting in adulthood.

Effects of GH replacement on BMD in GHD adults:

Growth hormone influences bone mass through direct and indirect actions (mediated through paracrine/endocrine IGF-1) (7). Growth hormone deficiency is associated with lower BMD in trabecular and cortical bone (4). Adults with GHD of childhood onset appear to have lower BMD than patients with adult onset GHD (8). Adults with more severe GHD [based on lower peak GH levels on stimulation testing or lower IGF-1 standard deviation scores (SDS)] may have lower BMD (9, 10). It has also been suggested that unreplaced sex steroid deficiency and corticotropin deficiency may be associated with lower BMD in GHD adults (10).

Growth hormone replacement in adulthood leads to increased bone turnover with a net positive effect on bone mass, resulting in increased BMD after 18-24 months (11, 12). Several studies suggest that the effect on BMD in the lumbar spine (LS) is greater than the effect on BMD in the hip (11-13). A positive effect on BMD has been sustained after 15 years of GH replacement in the LS, but not in the hip (possibly reflecting the inability of long-term GH replacement to prevent age-related bone loss) (13). It is also not clear if adults of both genders may benefit from GH replacement to the same extent with regards to BMD increase. Some, but not all, studies suggest that men may show a greater increase in BMD than women in response to GH replacement (11, 13, 14). However, it is possible that oral estrogen replacement may have limited the effect of GH replacement in women in some studies. Whether GH replacement leads to a decrease in fracture risk has not been examined in randomized clinical trials.

Metabolic effects of GH replacement in adults:

Growth hormone replacement leads to beneficial effects on systemic lipid profile, including decreased total cholesterol and low density lipoprotein (LDL) cholesterol in adults (15). Such beneficial effects of GH replacement have been demonstrated even in patients receiving lipid lowering therapy with statins (16). Growth hormone-replaced adults with craniopharyngioma appear to experience similar improvement in total and LDL cholesterol in comparison with patients with non-functioning pituitary adenoma (17). In contrast, there appears to be little or no effect of GH replacement on serum triglycerides or high density lipoprotein (HDL) cholesterol (15).

In addition, GH replacement decreases highly sensitive CRP in adults, which serves as a marker of systemic inflammation, thus potentially exerting an anti-atherogenic effect (18). Other possible salutary effects of GH replacement include beneficial effects on endothelial and cardiovascular function as well as decreased intima media carotid thickness (1, 19). It is not known whether such positive effects of GH replacement on cardiovascular biomarkers translate into blunting of the increased cardiovascular risk of hypopituitary adults.

Variable effects of GH replacement on glucose homeostasis have been observed. There appears to be a small increase in fasting glucose and insulin levels in adults on GH replacement, likely reflecting a GH mediated decrease in insulin sensitivity (15). However, the magnitude of this effect is generally small and often transient, as beneficial effects of GH replacement on visceral adiposity and fat free mass may translate into subsequent improvements in insulin sensitivity. Overall, there may be a small increase in the risk of development of diabetes mellitus in adults receiving GH replacement (20, 21). However, patients with higher baseline body mass index (BMI) appear to be at greater risk for developing diabetes mellitus and may require closer monitoring of glycemia (21).

Effects of GH replacement in young adults with childhood onset GH deficiency:

A subset of patients with childhood onset GHD has persistent GHD when retested after the completion of statural growth. Patients with organic or genetic causes of hypopituitarism are more likely to have persistent GHD in adulthood than those with idiopathic GHD of childhood onset. A discussion of the diagnosis of GHD in young adults in transition is beyond the scope of this presentation and has been published elsewhere (1, 22, 23).

Most, but not all, controlled trials suggest that GH replacement increases BMD in the LS of young adults with persistent GHD of childhood onset (24-27). In addition, beneficial effects of GH replacement on fat mass and fat free mass as well as serum lipids have been published (28).

Case presentation:

A 23 yr man with history of craniopharyngioma and panhypopituitarism of childhood onset came to our adult neuroendocrine clinic to establish care.

He had presented at age 15.5 yr with peripheral vision loss and delayed puberty. A predominantly cystic sellar lesion was noted on magnetic resonance imaging (MRI), impinging on the optic apparatus. He underwent complete resection via craniotomy. Pathology was consistent with craniopharyngioma (adamantinomatous type). His vision improved postoperatively. Laboratory testing showed panhypopituitarism. He was prescribed replacement therapies, including prednisone, levothyroxine, testosterone and desmopressin. In addition, he received GH replacement between age 16.5 and 18.5 yr and grew 12 inches.

After discontinuing GH replacement, he noted a decrease in stamina and muscle development despite regular exercise. He had continued on glucocorticoid (prednisone 4 mg orally daily), thyroid (levothyroxine 175 mcg orally daily), testosterone (1 % gel, 5 g topically daily) and desmopressin (10 mcg nasally at bedtime). Periodic regular MRI examinations of the brain revealed no evidence of tumor recurrence. His BMD was measured by dual energy X-ray absorptiometry (DXA) and was low for age (lumbar spine Z score: -3.3; femoral neck Z score: -2.3).

Laboratory testing showed insulin-like growth factor 1 (IGF-1) level of 76 ng/ml (normal range, 182 – 780 ng/ml); free thyroxine (T4): 1.1 ng/dl (normal range, 0.8 - 1.8 ng/dl); testosterone: 496 ng/dl (normal range, 270 - 1070 ng/dl); glycohemoglobin A1c: 5.6 %; total cholesterol: 162 mg/dl; LDL cholesterol: 92 mg/dl; HDL cholesterol: 59 mg/dl; triglycerides: 54 mg/dl. His peak GH level was 0.7 ng/ml on stimulation testing (using growth hormone releasing hormone – arginine).

After discussion of risks and benefits of GH replacement, he was prescribed GH, titrated to normal IGF-1 levels. The following questions will be discussed during the session:

1. What are the data on predictors of BMD in adult GHD patients (including patients with GHD of childhood onset persisting in adulthood)?

2. What are the effects of GH replacement on BMD in adults (including patients with childhood onset GHD persisting in adult life)?

3. What are the metabolic effects of GH replacement on lipid profile, C reactive protein and glucose homeostasis?

Disclosure: Nicholas Tritos receives research support from Ipsen and Pfizer and is a consultant for Pfizer.

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Traumatic Brain Injury and Hypopituitarism

Christopher Thompson

Beaumont Hospital/RCSI Medical School, Dublin, Ireland

Published data suggests that traumatic brain injury (TBI) is a significant cause of hypopituitarism, with estimates ranging from 10-60%, according to severity of brain injury and method of pituitary evaluation. Our own data, based on screening with glucagon testing and confirming abnormalities with either ITT or synacthen/GHRH tests indicate that up to 30% of long term survivors of moderate/severe TBI have permanent pituitary damage, ranging from mild, asymptomatic abnormalities to severe panhypopituitarism. In contrast, recent Danish data, using robust methodology, has demonstrated much lower rates of abnormality in patients with milder TBI. Even if the lower estimates of the prevalence of post-TBI are true however, the vast numbers of patients with TBI present a large population at risk of hypopituitarism.

Pituitary damage seems to be vascular in aetiology, due to haemorrhage or infarction of the gland. Early endocrine changes include stress-related hyperprolactinaemia, diabetes insipidus, and hypogonadism, which is probably an adaptive response, and is seen in many acute illnesses in ICU. We have recently presented data which shows however that the usual acute stress-mediated rise in plasma cortisol does not always occur following TBI, and that 80% of patients have abnormally low glucocorticoid responses to TBI. This offers the possibility that steroid therapy may be useful adjunctive therapy in TBI, although this remains speculative.

There have been a small number of prospective studies which have documented the natural history of changes in pituitary function following TBI. Allowing for protocol differences, they all demonstrate that some patients with early pituitary dysfunction improve to normal secretory capacity, whereas new changes can occur anything up to six months after the initial insult. The need for hormone replacement should ideally therefore be re-evaluated at intervals.

Screening for pituitary dysfunction following TBI remains problematic. There are few reliable clinical indicators for which patients are at particular risk of permanent damage, and even fewer predictors of which patients do not need screening; the latter would be particularly useful given the huge potential burden of universal screening. A high index of suspicion and careful consideration of clinical clues such as menstrual irregularity, erectile dysfunction, fatigue and poor engagement with rehabilitation continue to be the most important stimulators for evaluation in most units.

Disclosure: Christopher Thompson has no relationships to disclose.

CUSHING DISEASE

Chair: Stephan Petersenn

Disclosure: Stephan Petersenn is a speaker and Advisory Board member for Ipsen, Novartis, and Pfizer.

How to Differentiate Central from Ectopic ACTH-Dependent Cushing's Syndrome

John Newell-Price

University of Sheffield, UK

Before any attempt to differentiate central (pituitary - Cushing's disease) from ectopic sources of ACTH it is essential to have complete confidence that active ACTH-dependent Cushing's syndrome is present.

The *a priori* chance of pituitary vs ectopic should be considered: in women this is 9:1, whereas in men it is closer 3:1. Ectopic ACTH may be divided in overt, where the source is obvious on initial diagnostic work up; covert, where the source is apparent on follow up; occult, where the source of ACTH is never found.

Differentiation of ectopic from pituitary sources may be straightforward in severe overt ectopic ACTH due highly active tumors such as small cell lung cancer, but small non pituitary neuroendocrine tumors – NETs - (carcinoids) may effectively behave as an 'ectopic pituitary' in presentation and in much biochemical work up. In general, pointers to an ectopic source in the history include short duration, severity, and severe biochemistry with fewer physical signs (i.e highly active ACTH secretion without time for the classic Cushing's phenotype to develop). Hypokalemia is present in around 75% of patients with ectopic ACTH due to NETs, and almost universal in those due to small cell cancer. In contrast hypokalemia is present in around 10% of patients with pituitary disease.

The best means of differentiation between pituitary and ectopic ACTH secretion remains bilateral inferior petrosal sinus sampling with CRH stimulation, with a diagnostic accuracy of around 95%. Where this is unavailable use of peripheral CRH testing, together with information from dexamethasone testing can be very useful: a concordant significant rise of ACTH and or cortisol after CRH, and suppression on dexamethasone testing in a woman with ACTH-dependent disease, especially if there is a >6mm lesion on pituitary MRI, makes Cushing's disease almost certain.

In ectopic ACTH imaging with high resolution CT is needed, and MRI may be useful to define pancreatic NETs. Scintigraphy with radiolabelled octreotide may be useful to confirm an anatomically defined lesion as the source of ACTH, and PET imaging may hold promise in the future.

Disclosure: John Newell-Price has no relationships to disclose.

Peri-operative Management of Patients with Cushing's Disease

Ashley Grossman

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

The current rate of normalisation of biochemical and clinical features for Cushing's disease by transsphenoidal surgery approaches 90% or above in major centres, but the optimal peri-operative management of these patients is still far from consensual. There have been certain units where pre-operative normalisation of the high cortisol levels was attempted with medical therapy, principally metyrapone, but the current operation and short length of stay has allowed the great majority of patients to undergo surgery without such preparation, except in the most severe cases. The question as to whether patients require peri-operative corticosteroid cover has been more controversial, and many centres, including my own, routinely administer parenteral hydrocortisone with the pre-medication and for 24h afterwards before then re-assessing cortisol status. However, where there can be close clinical supervision this may be unnecessary, and then the serum cortisol at 090.00h on the morning after operation can be used to define surgical success. It would be of value to organise a clinical trial to assess whether 24h peri-operative corticosteroid replacement has any clinical utility, as currently there are few data in the literature.

Cushing's disease is associated with a hypercoagulable state, originally noted to be associated with elevated factor VIII and von Willebrand factor, but probably involving other factors and most likely impaired fibrinolysis. The incidence of venous thrombo-embolism has been reported to be as high as 15% in patients with Cushing's syndrome, but is more likely to be in the region of 2-3%; nevertheless, this rate is sufficiently high to consider routine ant-coagulation for patients undergoing petrosal sinus sampling and especially pituitary surgery. The elevated coagulability persists into the immediate post-operative period, but may normalise by 6 months. It would be important to have guidelines for patient anti-coagulation for patients with Cushing's disease undergoing investigation and surgery.

Disclosure: Ashley Grossman is a speaker for HRA Pharma and Novartis.

Pregnancy and Cushing's Syndrome: A Preliminary Report

Susan M Webb, Francisca Caimari, Patricia Garbayo, Charlotte Steffensen, Alicia Santos, Rosa Corcoy and Elena Valassi

Dept. Endocrinology/Medicine, Hospital Sant Pau, IIB-Sant Pau, Centre of Biomedical Research on Rare Diseases (CIBERER Unit 747), ISCIII; Universitat Autònoma de Barcelona (UAB); Barcelona, Spain

In November 2012 we performed a literature search using Medline with the headings of "Cushing AND pregnancy", and came up with 552 references; two independent reviewers selected 288 articles after title and abstract. In this preliminary report, we summarize data of 158 references dating back to 1952, reporting 309 pregnancies in women diagnosed with Cushing's syndrome (CS) (68 since 1990 on 99 patients with 158 pregnancies). Around 50% were diagnosed during pregnancy.

The main causes of Cushing's syndrome were: a pituitary adenoma (28%), adrenal adenoma (45%) or carcinoma (14%), ectopic ACTH secretion (6%) and dependent on HCG (5%). Mean maternal age during pregnancy was 28.2 + 5.2 years

Maternal complications were frequent, with diabetes mellitus reported in 35%, hypertension in 72% and preeclampsia in 24% of patients. Medical treatment was initiated during pregnancy in 91 patients (ketoconazole in 20%, metyrapone in 46% and mitotane in 10%, and other drugs in 23%). Surgery was carried out in 82%: prior to pregnancy in 11%, during pregnancy in 31% and postpartum in 40% of cases.

Outcome of the newborn showed a high prevalence of prematurity (49%). Respiratory distress and intrauterine growth retardation were both reported in 14% of cases . Perinatal mortality was reported in 11% and miscarriages in 7%. Maternal mortality occured in 11% of reports, not necessarily related to pregnancy.

Conclusions: Pregnancy in women with a diagnosis of CS is associated with high maternal and fetal morbidity, mainly hypertension and prematurity. These data would justify setting up a database to collect more recent data on women with CS who become pregnant, with the aim of improving management and outcome.

Disclosure: The authors have no relationships to disclose. This presentation will include discussion of product(s) unlabeled (off-label) for use as approved by the FDA or by the equivalent regulatory authority in the country in which the studies or trials were performed.

AGGRESSIVE PITUITARY TUMORS

Chair: Luis Syro

Disclosure: Luis Syro has no relationships to disclose.

Aggressive Pituitary Adenomas

[1]**Kalman Kovacs,** [2]**Luis V Syro**

[1]Department of Laboratory Medicine, Division of Pathology, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada,
[2]Department of Neurosurgery, Hospital Pablo Tobon Uribe and Clinica Medellin, Medellin, Colombia

Approximately 70% of pituitary adenomas are expansively growing benign neoplasms with slow cell proliferation rate. They are not encapsulated but are well demarcated by a pseudocapsule consisting of adjacent compressed non-tumorous adenohypophysial cells, capillaries, fibroblasts and collagen fibers. Approximately 30% of pituitary adenomas are invasive. They spread into adjacent tissues, penetrate the sphenoid and cavernous sinuses and expand to suprasellar areas. Less than 1% of pituitary neoplasms are malignant and are regarded as carcinomas. According to the currently accepted classification, the diagnosis of carcinoma can only be made when distant cerebrospinal and/or systemic metastases are documented. Pituitary carcinomas produce most often PRL or ACTH. Very rarely, they may synthesize GH, TSH, FSH, LH or alpha subunit or they may be unassociated with secretion of adenohypophysial hormones.

Recently, the terms "aggressive pituitary adenoma" and "atypical pituitary adenoma" were introduced. According to our interpretation, they represent the same tumor type. In our view "aggressive pituitary adenoma" provides a more relevant name.

The questions can be asked: do aggressive pituitary adenomas represent a distinct entity and what are the criteria of their conclusive diagnosis.

We believe that the most important criterion of aggressive pituitary adenomas is the rapid cell proliferation rate. Aggressive pituitary adenomas are frequently macroadenomas, invasive, occur more often in younger patients and are associated with hormone secretion. However, evidence indicates that large tumor size, invasion, younger age, and hormone secretion may also be noted in patients with slowly growing pituitary neoplasm. Tumor size, invasiveness, age, gender, hormone secretion, hormone content, cellular pleomorphism and local symptoms such as headache, visual disturbances are not decisive diagnostic features of aggressive pituitary adenomas.

More work is needed to find specific biomarkers and molecular/genetic abnormalities which would permit to conclusively diagnose aggressive pituitary adenomas. These studies would be extremely important not only theoretically but also practically because it would make possible to identify those patients whose tumor is rapidly proliferating and have malignant potential. At present, we recommend the application of the Ki-67 nuclear labeling index. This is a simple immunohistochemical approach, reliable in most cases. If the Ki-67 nuclear labeling index is above 10%, the diagnosis of aggressive pituitary adenoma appears to be justified.

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Disclosure: The authors have no relationships to disclose.

Aggressive Pituitary Tumors: Clinical Markers

Niki Karavitaki

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

Pituitary tumors are generally considered benign lesions. However, a small percentage of them (which is still not clearly estimated) may show aggressive behaviour with continued growth posing significant difficulties in their management and dictating multimodality treatments. The early identification of aggressive potential is of major importance, as it will allow the earlier establishment of a therapeutic strategy aiming to improve the prognosis of these patients.

Clinical markers of aggressive pituitary tumors are not clearly defined. They can be both functioning or non-functioning and they usually affect younger patients. The data on the impact of patient sex or degree of hormonal activity (in functioning ones) are not consistent, although extreme elevations of the serum prolactin levels, in cases of prolactinomas, have been proposed as a potential marker. From the imaging point of view, invasion of the surrounding structures (cavernous sinuses, suprasellar cistern, hypothalamus, brain stem) and size at presentation have been suggested as indicators of aggressive behaviour, with the first parameter been the most frequently reported marker.

Based on the existing published literature, the prediction of pituitary tumor behaviour on the grounds of the clinical phenotype at presentation remains a challenge and valid prognostic indicators for each pituitary adenoma subtype are needed. Correlation with pathological/molecular markers in studies with long follow-up will provide robust protocols on the management of this rare entity.

Disclosure: Niki Karavitaki has no relationships to disclose.

MRI and Surgery in Aggressive Pituitary Adenomas

E Knosp, A Micko, St Wolfsberger, Ch Höfberger

Department of Neurosurgery, Medical University of Vienna, Vienna, Austria

Objective: Invasiveness into the space of the cavernous sinus (CS) is an important prognostic factor for surgical outcome and recurrence of pituitary adenomas. The aim of this prospective study was to evaluate invasion of the CS using endoscopic techniques and to compare these findings with MRi findings.

Methods: We evaluated 137 consecutive endoscopically operated pituitary macroadenomas with parasellar extension on at least one side and apply these observations to the previously described a 4-tiered classification based on coronal MRi of the sella. We analysed the radiological and/or endocrinological results as well as the histopathological parameters with biological relevance using the Mib-1 antibody and the MGMT expression.

Results: We found with increasing grades a higher likelihood of invasive growth into the space of the CS. In adenomas with grade 1 invasion occurred in only 1,5%. In grade 2 the CS was invaded in 10% and in grade 3 in 38%. All cases with grade 4, which is encasement of the intracavernous carotid artery, were invasive.

The proliferation markers in this whole group of macroadenomas showed a higher growth rate of 2,8% (mean) compared to microadenomas 1,7% (mean) demonstrating a more aggressive growth. Within the different grades of invasion, however, we could not find a stat. significant difference.

Conclusion: The proposed classification proved to be a reliable predictor of increasing likelihood of invasiveness with increasing grades of parasellar invasion seen in MRi. With increasing grades of invasion the GTR drops increasingly from 96% in grade 1 to zero in grade 4.

The immunhistological findings support that surgically observed invasiveness into the CS is correlated with higher growth rates in Mib-1 expression and may justify a more aggressive therapy in residuals.

Discussion: Tumor invasiveness is the most important prognostic factor for incomplete resection of pituitary adenomas. Hence, determination of invasiveness is an important prognostic factor for patient outcome, and the preoperative knowledge of invasiveness is crucial for surgical planning, for considerations about adjuvant treatments and for patient information. The microscope, however, provided only incomplete visualization of the cavernous sinus wall, and venous bleeding impeded the intraoperative judgment of invasiveness. With the advent of the endoscopice technique, a direct visual inspection of the complete medial cavernous sinus wall became possible.

We could now demonstrate a significantly lower rate of invasiveness in grade 2 and 3 adenomas than in our original study. The analysis of grade 3 adenomas showed a significant diversity within this grade.

The direct endoscopic visualization of the medial cavernous sinus wall proved the low rate of invasion in grade 1 and the permanent invasion in grade 4. In grades 2 and 3, however, the direct endoscopic view showed significant lower rates of invasion than previously found using the microscope.

To be able to compare invasive growth into the CS with MRi data, we prospectively surgical observation to predict invasiveness by radiological criteria, we and compared these with surgical observation seen trough the operating microscope. With endoscopic vs. 88% with microscopic evaluation ($p<0.001$). In grade 3, the difference was 37,9% vs. 86% (endoscopic vs. microscopic, $p=0.0002$). A further analysis of grade 3 adenomas showed a statistically significant (26,5% vs. 70,6%, $p=0.001$) difference between invasiveness into the superior than into the inferior compartment. No difference in the rate of invasiveness in adenomas with parasellar externsion grade 1 and 4.

Disclosure: The authors have no relationships to disclose.

HOT TOPICS

Chairs: Paolo Beck-Peccoz and Felipe Casanueva

Disclosure: Paolo Beck-Peccoz and Felipe Casanueva have no relationships to disclose.

STAT3 Induces Growth Hormone Expression in Pituitary Somatotroph Cells

Cuiqi Zhou, Song-Guang Ren, Roy Heltsley, Kolja Wawrowsky, Shlomo Melmed

Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA

Somatotroph pituitary adenomas, which clinically result in dysregulated growth hormone (GH) hypersecretion and acromegaly, comprise about 30% of all pituitary tumors. As proximal regulatory mechanisms enabling GH hypersecretion in somatotroph adenomas remain elusive, we studied intracellular mechanisms inducing adenoma GH expression.

We provide evidence that GH is a direct STAT3 target in rat somatotroph tumor cells. Increased STAT3 expression was observed in 23 human somatotroph adenomas compared with 31 non-functioning pituitary tumors and 2 normal pituitary tissues ($P<0.001$, t-test). STAT3 and GH abundance were concordant in 35 somatotroph adenomas ($P<0.05$, Pearson's $\chi 2$-test). Human pituitary tumor specimens were obtained from the Department of Pathology with Institutional Review Board approval. STAT3 specifically bound the rat GH promoter and induced GH transcriptional activity (~2-fold) as assessed by chromatin immunoprecipitation and luciferase reporter assays. STAT3 transfection increased GH mRNA and protein abundance in somatotroph GH3 stable transfectants (~1.7-fold), and GH induction was further enhanced (3-fold) by constitutively active STAT3, while strongly abrogated by dominant negative STAT3. Suppressing STAT3 by the specific inhibitor S3I-201 decreased GH expression and secretion in vitro, and also attenuated somatotroph xenograft tumor growth in vivo. Wistar Furth rats harboring somatotroph xenografts were intravenously injected with S3I-201 or vehicle (anaesthetized, n=15 per group) at 5mg/kg every 2-3 days for 2 weeks. Xenograft tumor volume of S3I-201 treated group was significantly reduced compared to vehicle-treated rats ($P<0.01$). Furthermore, GH induced STAT3 phosphorylation and nuclear translocation in somatotroph tumor cells, indicating a positive feedback loop of STAT3 and GH.

These results elucidate a novel molecular mechanism for GH hypersecretion in somatotroph adenomas, whereby abundantly expressed STAT3 induces GH expression and results in excess GH synthesis and secretion. These findings also indicate STAT3 as a potential therapeutic target to abrogate somatotroph tumor growth and dysregulated GH hypersecretion.

Disclosure: The authors have no relationships to disclose.

Completely Humanizing Prolactin Rescues Infertility in Prolactin Knockout Mice

K.A. Gregerson[1,2], N.D. Horseman[2], H.R. Christensen[2]

[1]James L. Winkle College of Pharmacy and [2]Dept. of Molecular and Cellular Physiology, University of Cincinnati, Cincinnati, Ohio, USA

A variety of fundamental differences have evolved in the physiology of the human and rodent prolactin (PRL) systems. Disruption (knockout) of either the PRL gene or its receptor (PRL-R) causes profound female reproductive defects at several levels (ovulation, implantation, lactation). The PRL gene in humans and other primates contains an alternative promoter, 5.8 kb upstream of the pituitary transcription start site, that drives expression of PRL in "extrapituitary" tissues where PRL is believed to exert local, or paracrine, actions. Several of these extrapituitary-PRL tissues serve a reproductive function (e.g., mammary gland and decidua), consistent with the hypothesis that local PRL production may be involved in, and required for, normal reproductive physiology in primates. Rodent research models have generated significant findings regarding the role of PRL in reproduction, but the rodent PRL gene differs significantly from the human, most notably lacking the alternative promoter. Understanding of the physiological regulation and function of extrapituitary PRL has been limited by the absence of a readily accessible experimental model, since the rodent PRL gene does not contain the alternative promoter. To overcome these limitations, we have generated mice that have been "humanized" with regard to the structural gene and tissue expression of PRL. Here, we present the characterization of these animals, demonstrating that the human PRL (hPRL) transgene is responsive to known physiological regulators (dopamine, estrogen) both in vitro and in vivo. Expressed in several extrapituitary sites (mammary gland, uterus, ovaries), the transgene product is fully active at both the mouse and human PRL-R. More importantly, the expression of the hPRL transgene is able to rescue the reproductive defects and prevent pituitary tumorigenesis observed in mouse PRL knock-out (mPRL–) mice, validating their usefulness in studying the function or regulation of this hormone in a manner that is relevant to human physiology.

Disclosure: The authors have no relationships to disclose.

Temozolomide and Aggressive Pituitary Tumours: Longer-Term Follow-Up

Ann McCormack[1,2], Gerald Raverot[3,4] on behalf of PITUI-CARE (PITUItary-Carcinomas and Aggressive adenomas REsearch group

[1]Department of Endocrinology, St Vincent's Hospital and Garvan Institute of Medical Research, Sydney, Australia. [2] Institut National de la Santé et de la Recherche Médcale, U1028, Université de Lyon, Lyon [1], Faculté de Médecine Lyon-Est, Lyon, France

Background: Temozolomide now has an established role in the treatment of aggressive pituitary tumours, but efficacy and safety data are limited to case reports and small series with short-term follow-up. Objective and Methods: To report longer-term followup data on a large international cohort of patients with aggressive pituitary tumours treated with temozolomide. Clinical and pathological data were collected from clinicians in France, Australia, Italy, UK and USA. Results: A total of 34 patients (25 male, 9 female) of mean age 52.7 years (24 adenomas, 10 carcinomas) of various subtypes (ACTH 14, PRL 13, PRL-GH 3, GH 2, NF 2) were studied. These tumours were clinically and pathologically aggressive: average number of surgeries 2.5 and radiotherapy courses 1.5, Ki67 >3% in 20/24 cases. Patients underwent an average of 8.9 cycles of temozolomide with 60% experiencing no adverse effects. A hormonal response was reported in 61%, and radiological response in 67.7%, all by 3 months of treatment except one case. Seventeen patients with response have been followed for a mean of 36 months. One responder had disease progression at 6 months on temozolomide, the remaining 16 completed treatment. Six remain stable off treatment (6-15 months) whilst 11 have developed recurrence between 4 months and 4 years later. In 3 patients, a second course of temozolomide was not successful. When trialed, subsequent treatment with pasireotide, everolimus or alternative chemotherapy was not effective. Six of 22 (27%) responding patients have died, compared with 8 of 12 (67%) non-responding patients. Conclusion: Amongst this large cohort of aggressive pituitary tumours, the use of temozolomide is associated with high initial response rates, and commonly stable disease for many months after treatment cessation. Unfortunately, tumour re-growth ultimately occurs in the majority of responding patients. This study suggests that mortality may be reduced in patients who respond to temozolomide.

Disclosure: The authors have no relationships to disclose.This abstract 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.

Novel and Highly Sensitive EIAs for the Differential Diagnosis (DDx) Between Cushing's Disease (CD) and Ectopic ACTH Syndrome (EAS)

Katakami H[1], Hashida S[2], Miyamura N[3], Matsuno A[4], Hizuka N[5], Yamada S[6]

[1]Div. Clin. Res. Sci, Dpt. Med. &[4]Dpt. Neurosurgery, Teikyo Univ. Chiba Med. Cnt, Ichihara, Japan 299-0111, [2]Inst. Human Health Sci, Tokushima Bunri Univ., Tokushima, Japan, [3]Dpt. Med., Kumamoto Univ., Kumamoto, Japan, [5]Dpt Med, Tokyo Women's Med. Univ., Tokyo, Japan, [6]Dpt. Hypothalamic and Pituitary Surgery, Toranomon Hsp., Tokyo, Japan

Table 1

EIAs & RIAs LDV (fg/tube)* ①: epitope	γ1-MSH RIA 100fg* ① γ1-MSH 1-11 pro γ3-MSH	γ3-MSH RIA 100fg* ① γ3-MSH 1-17 pro γ3-MSH	ICT-EIA I 1fg* ON: 1-24 OC: 18-39	ICT-EIA II 1fg* ON: 1-10 OC: 18-39
POMC, 241aa γ1-MSH 1-11 γ3-MSH 1-17 Pro-ACTH ACTH 1-39 N-POMC, 76aa (pro γ-MSH) ACTH 1-39aa	○	○	△	○
	○	○	△	○
	○	○	×	×
	×	×	○	○

Fig.1

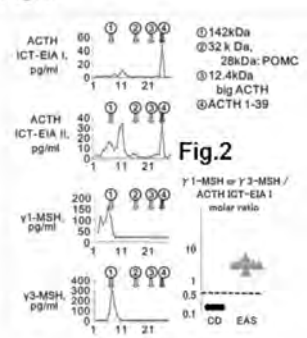

Fig.2

EAS is composing 10% of Cushing's syndrome. Despite advances in modern technologies, EAS has been one of the most challenging diseases in Endocrinology. POMC processing is on the other hands deviated, and production of N-terminus forms of POMC is increased in EAS.

We therefore developed highly sensitive EIAs and RIAs to detect circulating precursor forms of POMC, i.e., gamma 1-/gamma 3-MSH and big ACTH for DDX between EAS and CD (Table 1).

Controls (11 males, 15 females, age 25-55), CD (6 males, 9 females, age 30-75), EAS (GEPNET etc., 4 males, 7 females, age 40-75). ACTH EIA I, ACTH EIA II (big ACTH as well as ACTH1-39), LDV 1.0fg, gamm1-MSH RIA, gamma3-MSH RIA. qRT-PCR: POMC/beta-actin, PC1/PC3/beta-actin.

Plasma levels of N-terminus forms of POMC, as assess by gamma1-MSH/gamma3-MSH and ACTH EIA II were low in controls. Patients with CD (micro ACTHoma) showed higher plasma ACTH levels, but lower or undetectable plasma levels of gamma1-/gamma-3 MSH. By contrast, plasma big ACTH and pro-gamma 3-MSH leves, as assessed by HPLC (Fig. 1), were increased. The molar ratio of gamma1- or gamma3-MSH / ACTH EIA 1 was therefore over 0.5 (cut off ratio, Fig.2). Gene expression of POMC and PC1/3 were increased and decreased, respectively, in tissures from EAS. These results suggest higly sensive EIA and RIAs for N terminus precussors of POMC are useful for DDX between EAS and CD.

Disclosure: The authors have no relationships to disclose.

DEBATE

Cushing Treatment

Moderator: Jérôme Bertherat
Disclosure: Jérôme Bertherat has no relationships to disclose.

This debate may include discussions 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.

Cushing Treatment Debate: Pituitary Targeted Medical Therapy or Radiation?

Marco Boscaro

Division of Endocrinology, Polytechnic University of Marche, Ancona, Italy

Cushing's disease (CD) results from a chronic excess of cortisol caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma.

It is important to treat patients with CD early to minimize long-term mortality and morbidity.

Selective transsphenoidal pituitary adenomectomy remains the treatment of choice for CD but, the rate of cure at long-term follow-up is suboptimal and recurrence can occur even following expert surgery.

Second-line options include repeat pituitary surgery, medical treatment, radiation therapy and bilateral adrenalectomy.

Pituitary directed treatment may be the treatment of choice in patients with persistent or recurrent CD with the aim to control hypercortisolism directly acting to the pituitary tumor and thus to the source of ACTH hypersecretion.

About medical treatment, in the last years several novel therapies have been studied and developed.

In a subset of patients with persistent or recurrent CD (~30%), long-term treatment with cabergoline has been associated with a normalization of urinary free cortisol (UFC) levels and tumor shrinkage. Cabergoline has also been described as having potential positive metabolic effects (pressure lowering, improvement of glucose tolerance), independently of its cortisol lowering effect. Unfortunately, a significant number of patients showed a treatment-escape to cabergoline treatment, even after several years of treatment.

Recently, the multireceptor-targeted somatostatin analogue pasireotide has been EU-approved for the treatment of CD in patients not suitable for surgery or in whom surgery has failed. The results of a proof-of-concept study and those of a recently published Phase III study showed in fact the efficacy of this drug in patients with CD in reducing biochemical markers as well as in improving signs and symptoms of hypercortisolism regardless of UFC normalization. Pasireotide treatment has been also associated with a significant tumor shrinkage. The safety profile of pasireotide is similar to that of other somatostatin analogues, with the exception of the incidence of hyperglycaemia, that however may be easily managed.

Finally in the context of pituitary-directed drugs a promising option seems to be represented by retinoic acid. More recently in fact a prospective multicenter study even if limited to a small number of CD patients showed positive results. However these data need confirmation in larger series.

Pituitary radiotherapy (conventional fractionated radiotherapy or stereotaxic radio surgery) represents also a pituitary-targeted option in patients with recurrent or persistent CD. However, radiotherapy acts gradually on the tumors and so medical treatment is needed waiting for its beneficial effects. Success rates in controlling hypercortisolism are very different between series and the incidence of therapy-induced pituitary failure is significant (~50%) appearing to be similar with radiotherapy or radiosurgery. Radiotherapy has been also associated with a potential risk of cerebrovascular and neurocognitive complications that seems however to be reduced with modern radiotherapy techniques.

Pituitary radiotherapy seems to be a second line option in respect to medical treatment in patients with persistent or recurrent CD.

Disclosure: Marco Boscaro has no relationships to disclose.

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What's Next After Failed Pituitary Surgery for Cushing's Disease: Medical Therapeutic Approaches

Maria Fleseriu

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

Recent evidence supports the notion that the incidence of Cushing disease is higher than previously thought. Transphenoidal surgery is the treatment of choice, but many patients require additional treatment.

Pituitary-targeted therapies may provide both an anti-secretory and an anti-proliferative treatment. Dopamine agonists have demonstrated some efficacy in small proof-of concept or retrospective studies. Pasireotide, recently FDA and EMA approved, is a multi-receptor SRL with high binding affinity to sst5, the receptor predominantly expressed in corticotroph adenomas. In a large prospective study, 14.6% and 26.3% of patients normalized UFC at 6 months for the 600-μg and 900-μg doses, respectively. Clinical improvement (blood pressure, body weight, quality of life- QoL) was evident in most patients. Importantly, lack of response could be usually identified within 2 months. With the exception of the degree and severity of hyperglycemia, adverse effects were similar to other SRLs. Optimal management of hyperglycemia in patients treated with Pasireotide needs further research.

Medications suppressing adrenal steroidogenesis currently in use include ketoconazole, metyrapone, mitotane, or etomidate. In addition, the investigational agent LCI699 is under research.

Mifepristone (a glucocorticoid receptor antagonist) has been recently FDA- approved for treatment of hyperglycemia associated with Cushing's syndrome. In a 6-month open- label trial on doses of 300 - 1,200 mg, 60 % of patients with glucose intolerance or diabetes had at least 25 % reduction in glucose on OGTT. Several clinical parameters and QoL also improved significantly. Adverse effects included hypokalemia, and endometrial thickening with vaginal bleeding. The lack of a biochemical marker dictates that efficacy and adrenal insufficiency assessments should be based on symptoms, clinical and metabolic features.

Current data, though still limited, indicate that a multimodal pharmacologic treatment approach may offer additive or synergistic clinical benefit with acceptable tolerability. The merits and pitfalls of each class of therapy will be further reviewed. Individual selection depends on drug approval and availability in each country and requires cautious evaluation of efficacy, potential adverse effects and co-morbidities.

Disclosure: Maria Fleseriu's institution has received research support from Novartis and Corcept and she is a consultant for Novartis.

Options After Initial Surgical Failure: *If At First You Don't Succeed…*

Brooke Swearingen

Department of Neurosurgery, Massachusetts General Hospital, Boston, Massachusetts, USA

Surgery remains first-line treatment for Cushing's disease with success rates of 70-90% depending upon the series, with remission as a function of tumor size and MRI findings. The recurrence rate is about 10% at 5 years; approximately 2% per year. Early reoperation is successful in achieving remission in 50-70% of cases, as is surgery for recurrence, with some increased risk of hypopituitarism. Adrenalectomy leads to resolution of hypercortisolemia in almost all cases, but requires lifelong gluco- and mineralocorticoid replacement, as well as a risk of corticotroph tumor progression over time. We will discuss these options.

Disclosure: Brooke Swearingen is a consultant for Novartis, and owns stock in Amgen, Novartis, Pfizer and Roche.

DEBATE

Acromegaly Treatment

Moderator: Christian Strasburger

Disclosure: Christian Strasburger is an Advisory Board member for Chiasma, Lilly, Novartis, Pfizer, Serono, and Sandoz, and is a Speaker/Chairperson for Ipsen, Novo Nordisk, and Pfizer.

This debate may include discussions 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.

Medical Treatment of Acromegaly

John Ayuk[1], Vivien Bonert[2], Philippe Chanson[3], Christian Strasburger[4]

[1]Queen Elizabeth Hospital, Queen Elizabeth Medical Centre, Birmingham, UK, [2]Cedars-Sinai Medical Center, Los Angeles, California, USA, [3]AP-HP, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, Paris, France, [4]Charité Universitätsmedizin, Campus Mitte, Berlin, Germany

Therapies for acromegaly aim to control tumor growth, inhibit GH hypersecretion, and normalize serum IGF-I levels. The three therapeutic modalities employed, include surgery, medical management, and radiotherapy. This debate focuses on the three classes of medical therapy: dopamine agonists (parlodel, cabergoline), somatostatin analoges, SSAs (octreotide, lanreotide) and the GH receptor antagonist (pegvisomant).

Medical therapy is most frequently used as adju¬vant treatment in those patients with persistent disease after primary surgical therapy. A role of primary medical therapy, especially with somatostatin analogues (SSAs), has been suggested in patients with macroadenomas without local mass effects, who have a minimal chance of surgical cure (because of extrasellar extension of the tumor, espe¬cially into the cavernous sinus) or in patients who are poor surgical candidates or who prefer medical treat¬ment.

The risks and benefits, strengths and weaknesses of the three classes of medical therapies will be debated, including efficacy, side effects, cost of therapy and factors influencing compliance.

Disclosure: John Ayuk has no relationships to disclose, Vivien Bonert is a consultant for Ipsen and Pfizer, and Philippe Chanson is a consultant, speaker, teacher, Advisory Board member, and investigator for Ipsen and Novartis, and Pfizer, and is an investigator for Orion.

Acromegaly Debate: Treatment with Cabergoline

Philippe Chanson

Endocrinology and Reproductive Diseases, Hôpital de Bicêtrel and Université Paris-Sud, Le Kremlin-Bicêtre, France

Cabergoline, an ergot derivative dopamine agonist, has been used for three decades in the treatment of Parkinson's disease and hyperprolactinemia. Being more effective and better tolerated than bromocriptine, cabergoline was also tested as a treatment for acromegaly, but its potential value was overshadowed by the advent of somatostatin analogues, which were shown to normalize IGF-I in 42-68% of patients [1-4]. By comparison, bromocriptine was considered to normalize GH/IGF-I levels in only around 10% of cases [5]. Clinical trials of cabergoline in acromegaly were mostly small and gave variable results [6-17]; a larger trial [7] suffered from a failure to use age-adjusted normal IGF-I values. Moreover, none of these trials was randomized or placebo-controlled. Moreover, none of these trials was randomized or placebo-controlled. This led to the general opinion that cabergoline was poorly effective, or that it was only effective in patients with mild residual disease or mixed GH/PRL-secreting tumors. We thus systematically reviewed all trials of cabergoline therapy for acromegaly published up to 2009 and identified 15 studies (11 prospective) with a total of 237 patients; none were randomized or placebo-controlled. A meta-analysis was conducted on individual data (n=227). Cabergoline was used alone in nine studies. Fifty-one (34%) of the 149 patients achieved normal IGF-I levels. In multivariate analysis, the decline in IGF-I was related to the baseline IGF-I concentration (ß = 1.16; P < 0.001), treatment duration (ß = 0.28; P < 0.001), and baseline prolactin concentration (ß =0.18; P < 0.01), and with a trend toward a relation with the cabergoline dose (ß = 0.38; P < 0.07). In five studies, cabergoline was added to ongoing somatostatin analog treatment that had failed to normalize IGF-I. Forty patients (52%) achieved normal IGF-I levels. The change in IGF-I was significantly related to the baseline IGF-I level (ß = 0.74; P < 0.001) but not to the dose of cabergoline, the duration of treatment, or the baseline prolactin concentration [18].

The main concern with cabergoline treatment is its potential adverse effect on cardiac valve. The effects of cabergoline on cardiac valves have been extensively studied in Parkinson's disease and hyperprolactinemia but not in acromegaly, a condition at risk of cardiac valve abnormalities. Recently, we thus decided to examine the prevalence and incidence of heart valve disease and regurgitation in a series of patients with acromegaly treated with cabergoline, by comparison with matched patients who had never received this drug. We conducted a cross-sectional and longitudinal study in our single center, at Bicêtre' hospital in Paris [19]. Forty-two patients who had received cabergoline at a median cumulative dose of 203 mg for a median of 35 months were compared to 46 patients with acromegaly who had

never received cabergoline and who were matched for age, sex, and disease duration. A subgroup of patients receiving cabergoline (n = 26) was evaluated longitudinally before and during cabergoline treatment and compared to a group not receiving cabergoline and followed during the same period (n=26). Two-dimensional and Doppler echocardiographic findings were reviewed by two cardiologists blinded to treatment. Demographic and clinical features were not significantly different between the groups. Compared to acromegalic controls, patients receiving cabergoline did not have a higher prevalence or incidence of valve abnormalities.

In conclusion, cabergoline single-agent therapy normalizes IGF-I levels in one third of patients with acromegaly and when a somatostatin analog fails to control acromegaly, cabergoline adjunction normalizes IGF-I in about 50% of cases. This effect may occur even in patients with normoprolactinemia. Finally, cabergoline therapy is not associated with an increased risk of cardiac valve regurgitation or remodeling in acromegalic patients at the doses used in our study.

Disclosure: Philippe Chanson is a consultant, speaker, teacher, Advisory Board member, and investigator for Ipsen, Novartis, and Pfizer, and is an investigator for Orion.

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POSTER PRESENTATIONS

Acromegaly

P1

An Observational, Comparative Trial in Patients with Active Acromegaly Receiving a New Long-acting Octreotide Formulation Who Were Previously Treated with the Original Octreotide Formulation (Sandostatin LAR)

Wilson Gallardo

Guillermo Almenara National Hospital, Perú

Summary: Surgery is choice therapy for acromegaly; its success rate is only ~50%. Historically, patients who failed surgery have been treated with the original formulation of octreotide acetate, which has a well-established efficacy and safety profile. Recently, a new long-acting octreotide formulation has been introduced in the Peruvian market; however, this compound does not currently have any evidence base to support its efficacy and safety. Objective: Evaluate the outcomes of patients with active acromegaly treated with new long acting octreotide 20 to 40 mg/month for at least 8 months, who had previously received Sandostatin LAR 20 to 40 mg/month. Eighteen patients, all of whom had previously undergone surgery and radiotherapy, were enrolled at G. Almenara National Hospital. Fifty-six percent of patients were male; average age ± SD was 49.2 ± 13.6 years (range 30–77); average time with acromegaly disease ± SD was 12.8 ± 5.4 years (range 4–25). Following a two-month washout from previous Sandostatin LAR treatment, patients were treated with new long acting octreotide. Of the 18 patients enrolled, 77.8% (n=14) had normalized insulin-like growth factor 1 (IGF-1) values when they finished therapy with Sandostatin LAR. However, following treatment with new long acting octreotide , only 38% (n=7) of patients had normalized IGF-1. The clinical course of patients did not improve with the new long acting octreotide and was observed no reduction of tumor volume. Overall, 44.4% of patients (n=8) receiving new long acting octreotide experienced adverse events, which is twice the amount observed during Sandostatin LAR treatment, 22.2% (n=4). **Conclusions:** 1) Patients had substantially better IGF-1 control and experienced fewer adverse events when treated with original octreotide formulation compared with the new long acting octreotide formulation. 2) Due to the small number of patients enrolled in this trial, additional studies are required in order to better establish the efficacy and safety of this new long acting octreotide formulation in patients with acromegaly.

Disclosure: Wilson Gallardo has received consulting fees from Novartis.

P2

Colonic Neoplasia in Acromegaly

Battistone, María Florencia ; Garcia Basavilbaso, Natalia; Szuman, Grabriela; Guitelman, Mirtha

Department of Endocrinology, Durand Hospital, Buenos Aires, Argentina

Introduction: Several studies have suggested that acromegalic patients have a high prevalence of colorectal neoplasias, although the degree of risk still remains under debate. A meta-analysis which included 701 patients showed that the frequency of colon hyperplastic polyps, colon adenomas and colon cancer in acromegalic patients was 22.3%, 23.3% and 4.6% patients respectively. **Objectives:** to evaluate the presence of colonic neoplasias in a subset of patients with acromegaly, to correlate it with clinical and biochemical characteristics and compare our results with those reported in the literature. **Material and methods:** 40 patients with acromegaly age 43,54 ± 14,44 (X ± ds), (29 females) were retrospectively evaluated with at least one surveillance videocolonoscopy (VCC). Age, gender, basal IGF-1 levels, status of the disease at time of VCC, duration of acromegaly and familiar history of colonic pathology were analyzed. Unpaired T test and fisher test were performed for between-group comparison. **Results:** 21 out of 40 patients (52.5%) were found to have a normal VCC (-) while 19 (47.5%) presented a pathologic VCC (+). Hyperplastic polyps, adenomas and colon cancer were found in 8 (20%), 8 (20%), and 3 (7.5%) patients respectively; a similar frequency reported in the literature. There were no statistically significant differences in any of the clinical and biochemical characteristic analyzed between both groups. **Conclusion:** half of a subset of acromegalic patients in our study had colonic neoplasia. Duration of acromegaly and basal IGF-1 levels seem to be variables that do not increase the risk of colonic neoplasia. Screening with colonoscopy should be indicated in acromegalic patients at diagnose, at any age and at any stage of the disease based in our results and those reported in the literature.

Disclosure: The authors have no relationships to disclose.

P3

Combination Therapy in Patients with Acromegaly Partially Responsive to Somatostatin Receptor Ligands (SRL): Decreasing SRL Dose When Adding Pegvisomant (PEG), A Case Series

Jessica Brzana*, Chris Yedinak and Maria Fleseriu

Northwest OHSU Pituitary Center, OHSU School of Medicine, Departments of Medicine and Neurological Surgery, Portland, Oregon, USA

INTRODUCTION: SRL/PEG combination therapy has been shown to control disease activity in acromegaly patients partially resistant to SRL maximum dose monotherapy. It may also impact tumor rebound after SRL withdrawal and improve glucose metabolism. **OBJECTIVE:** To determine if SRL/PEG combination could achieve disease control with overall dose reduction if SRL dose is decreased when PEG is added. METHOD: A retrospective chart review of all OHSU patients with acromegaly on combination PEG/SRL after failed pituitary surgery (2007-2012) was undertaken. **RESULTS:** Eight patients resistant to maximum monthly dose of lanreotide 120 mg or octreotide LAR 40 mg were identified; 2 with history of radiation excluded. 2M/4F, age at diagnosis: 28.5 ± 6.3 years. Average follow-up: 68.3 ± 43 months. All macroadenomas, 3 with residual tumor post-op. Pathology confirmed somatotroph adenoma, 4 SSTR2A+. Mean postoperative IGF-1 (ng/mL): 1.88 x ULN ±0.58. Mean SRL dose: octreotide 40 mg (median 40) or lanreotide 105 mg ± 21.2 (median 105). Mean IGF-1 on SRL: 1.44 X ULN ± 0.50. After addition of PEG mean 16 ± 8.8 mg/day (median 15;4.3-30), octreotide and lanreotide were reduced to 20 mg (median 20) and 76mg ± 15 (median 80). IGF-1: 0.80 X ULN ± 0.19. Liver function tests were normal, glucose control and tumor size remained unchanged. **DISCUSSION:** SRLs were recently shown to control GH secretion in 20-40% of patients and tumor shrinkage in up to 75%. For patients failing maximum SRL dose, we added low-dose PEG while reducing SRL dose. This regimen was both successful and well tolerated in all patients. Final PEG dose was lower than described for monotherapy. **CONCLUSION:** In our cohort of partially SRL resistant radiation naïve patients, combination PEG/SRL therapy normalized IGF-1 without additional side effects and SRL and PEG doses were reduced. Optimal dosing regimen for safety and cost reduction requires further study.

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P4

Does Clinical Trial Methodology Determine Biochemical Efficacy of Somatostatin Receptor Ligand Therapy in Treatment of Acromegaly?: A Meta-Analysis

John D. Carmichael; Vivien Bonert; Miriam Nuño, PhD; Diana Ly; Shlomo Melmed

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

Introduction: Efficacy of somatostatin receptor ligand (SRL) treatment in acromegaly is generally defined in terms of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) control. However, biochemical control criteria, medical formulations, and assay techniques have evolved since the earliest trials more than 30 years ago. We therefore evaluated how variation in such clinical trial methodologies affect reported GH and IGF-1 outcomes. **Methods:** We searched PubMed for English-language trials published from 1974–2012 evaluating 10 or more patients, with duration longer than 3 months and biochemical control as a key objective. Case series/reports studies were excluded. We compared biochemical outcomes between short- and long-acting formulations of octreotide (OCT) and lanreotide (LAN) trials for parameters (study design/duration, baseline demographic/clinical characteristics, prior treatments, SRL formulation/dosing, assay methodology, biochemical control definition) while adjusting for within-study correlation. **Results:** 103 studies published between 1987 and 2012 and including 5,185 patients were analyzed. OCT and LAN trials comprised 52% and 41%, respectively. Overall GH control rate (mean±SD) was 56%±20; IGF-1 normalization, 53%±18. Biochemical control was directly related to cohort age ($p<0.001$), size ($p<0.001$), study duration ($p<0.001$), use of fixed-then-titrated dosing ($p<0.0001$), and prior SRL therapy ($p<0.001$). After multivariate analysis (entry value <0.05), SRL type did not significantly influence response ($p=0.88$). There were no significant relationships between response rate and publication date, retrospective vs. prospective design, use of switch-study design, or short- vs. long-acting formulations. **Conclusions:** Reported outcomes for SRL treatment are influenced by many factors. Multivariate analysis revealed age to be the single most significant predictor of GH and IGF-I control. In univariate analyses, factors expected to impart favorable outcomes (e.g., study publication date, switch-study design, use of long-acting formulation) did not have statistically significant influence on reported control rates.

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P5

Evolution of a Silent GH Pituitary Adenoma (PA) to an Aggressive GH Secreting Tumor After Pregnancy

Fainstein Day P, Glerean M, Canteros TM, Lovazzano S

Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Introduction: Less than 20% of GH secreting PA has an aggressive clinical behavior. Estrogen receptors (ERs) would promote invasiveness in NFPA downregulating Slug-E-cadherin expression. **Clinical Case:** A 26 year-old female patient presented with oligomenorrhea and galactorrhea. She showed slightly elevated prolactin levels and normal IGF-1 levels. MRI showed a PA with suprasellar extension. Visual field (VF) was normal. A diagnosis of NFPA was made. Pathology studies showed a immunohistochemically (IH) positive for GH adenoma and Ki-67 of 7%. Part of PA remained after TSE surgery. She improves clinically. On Dec, 2008 she became pregnant. She complained of headaches and visual disturbances during the 3rd trimester of pregnancy. VF showed mild bilateral scotomas. After a normal delivery on Sept 2009, the patient developed clinical symptoms of acromegaly and biochemical results were consistent with this diagnosis. A new TSE surgery was made. New pathologic studies showed a sparsely granulated GH adenoma with Ki-67 of 7% and moderate expression of p53. ERs were strongly expressed and no E-cadherin expression was found.

	Basal	Post 1st surgery	6 m post partum	Normal ranges
Prolactin	52	12.9	24	5-25 ng/mL
GH	5.1	1.9	4.5	ng/ml
IGF-1	200	200	780	95-400 ng/mL
OGTT/GH			4.5/3.5/3.1/ 3.0/2.4/2.5	< 1.0 ng/mL
FT4	1.1	1.1	1.5 on LT4 treatment	0.8-1.8 ug%

Conclusions: This is a young woman with an initially silent GH PA that evolved to an aggressive GH secreting PA during pregnancy. Strong IH expression of ERs associated to absence of E-cadherin expression in tumor tissue suggests a role of high circulating E2 levels in tumor pituitary evolution.

Disclosure: The authors have no relationships to disclose.

P6

Influence of Tumor Volume and Cavernous Sinus Invasion on Hormone Levels and Remission Following Endoscopic Transsphenoidal Surgery for Acromegaly

Adam N Mamelak; Michael Schiraldi; Miriam Nuño; John D Carmichael; Vivien H Bonert; Shlomo Melmed

Pituitary Center, Departments of Neurosurgery and Endocrinology, Cedars-Sinai Medical Center, Los Angeles, California, USA

Objective: To determine factors that influence outcome following endoscopic transsphenoidal surgery in acromegaly patients. **Methods:** Retrospective analysis of our IRB approved registry identified acromegaly patients undergoing endoscopic pituitary surgery by a single surgeon (ANM). Three-dimensional tumor volumes were calculated from coronal gadolinium enhanced MRIs (2-3 mm slice thickness) using the "closed polygon" algorithm of a DICOM software program (Osirix). Knosp (K) scores, a measure of cavernous sinus extension, were determined by visual inspection of coronal images. Patients with extensive cavernous sinus extension are routinely treated with primary medical therapy at our center and not treated with surgical debulking. Pre-operative IGF-1 and basal (bGH) and nadir (nGH) growth hormone levels during OGTT were recorded. Patients were considered in remission based on post-operative criteria of normal IGF-I and nGH < 0.4ng/ml. Data was subjected to multivariate analysis using ANOVA and univariate comparison to surgical outcome (SPSS software). **Results:** 50 patients underwent surgery for acromegaly with curative intent between 2006 and 2012, with long-term follow-up available in 46 patients. Remission was achieved in 36 (78%) patients (observed up to 7 years post-operatively, mean 3.7 years.) Age at diagnosis significantly predicted surgical cure, with older patients having a higher remission rate (mean age 52.6 years vs. 37.9 years; p=0.002). There was no significant correlation between K-score and preoperative GH or IGF-I levels. Neither tumor volume nor K-score correlated with remission, indicating that endoscopic removal may be equally effective at removing microadenomas and macroadenomas. There was no relationship between pre-operative IGF-1, bGH, or nGH and remission. Conclusions: Endoscopic transsphenoidal surgery resulted in a high surgical cure rate (78%). Tumor volume and invasiveness did not correlate with surgical cure. When compared to published data, these results suggest that endoscopy yields better outcomes than microscopy for acromegaly.

Disclosure: The authors have no relationships to disclose.

P7
Management of Pregnant Acromegalic Patients in LA: A Retrospective Study

Manavela M[1], Danilowicz K[1], Chervin A[2], Guitelman M[3], Mangupli R[4], Valenzuela A[5], Vitale M[2], Rogozinski A[6], Abreu Lomba A[7]

[1]Hospital de Clínicas, Universidad de Buenos Aires, Argentina; [2]Hospital Carlos G. Durand, Buenos Aires, Argentina; [3]Hospital Santa Lucía, Buenos Aires, Argentina; [4]Hospital Universitario de Caracas, Venezuela; [5]Hospital Universitario, Fundación Santa Fe de Bogotá, Colombia, [6]Hospital Ramos Mejia, Buenos Aires, Argentina; 7Centro Médico Imbanaco, Cali, Colombia

Introduction: there are few data about the effects of GH hypersecretion on the fetal and maternal evolution and the consequences of pregnancy on the tumor volume. **Patients:** we retrospectively analyzed 29 pregnancies of 21 active acromegalic patients from different Latin-American centers. Their average age was 29.3 yr (19-40 yr). Basal MRI showed microadenomas (n=2), macroadenomas (n=16), empty sella (n=2) and normal (n=1). Biochemical GH and PRL cosecretion were found in 9/21(43%) cases. Eighteen patients underwent surgery before pregnancy. At the moment of conception, 18 cases received medical treatment (6 dopamine agonist, 6 somatostatin analogs and 6 both) Five received treatment throughout their pregnancy (4 somatostatin analogs and 1 dopamine agonist). **Results:** 29 pregnancies were achieved in 21 patients (28 spontaneous and one through fertility treatment). The average time between the diagnosis of acromegaly and pregnancy was 3.7 years (3months - 12 years). There were 26 deliveries (21 at term, 4 preterm and 1 stillbirth) and 3 miscarriages. Deliveries by cesarean section occurred in 15 and by the vaginal route in 11 cases. Neither macrosomia nor malformations were observed. Gravid hypertension occurred in 5 pregnancies (17%), gestational diabetes in 6 (21%) and premature deliveries in 4 patients. Tumor size was stable in 18 (70%), increased in 4 (15%) and decreased in 4(15%). One patient developed visual field defects during pregnancy and was surgically treated. Normal children were born in 4/5 women who received medical treatment throughout their pregnancy, while one treated with somatostatin analogs had a miscarriage. **Conclusions:** pregnancy in active acromegaly patients may be associated with an increased risk of gestational diabetes and gravid hypertension, and is occasionally associated with symptomatic enlargement of the adenoma. Medical treatment of acromegaly throughout pregnancy, when necessary, seems to be safe and well tolerated.

Disclosure: The authors have no relationships to disclose.

P8
Medical Training Does Not Influence the Ability to Perform Successful Injections of Somatuline® Depot (SD; Lanreotide)

Susan L. Smith (RN, CNS, CDE, PNP),[1] Adam Shames (MS, MBA),[2] Fabien Jeannerot[1]

[1]Ipsen Biopharmaceuticals, Inc., Basking Ridge, New Jersey, USA; [2]Core Human Factors, Wynnewood, Pennsylvania, USA

Background: Long-acting Somatostatin Analog injections are administered by people with varying backgrounds from skilled medical professionals to those with no medical training. **Objectives:** To investigate the comprehension and skill level of Health Care Providers (HCPs) versus Non-Professional Caregivers (NPCs) using a simulated gel in a new somatostatin analog syringe with a passive integrated sharps protection system. **Methods:** Data from subjects in two human factors studies were analyzed according to the level of medical training, ie., HCP or NPC. Cohort 1 was trained before use of the device. Cohort 2 was asked to use the device untrained. Using an anatomical model and simulated product 19 parameters were assessed including 4 device tasks deemed critical for safe and effective use (preparation for injection through safe disposal), and 15 standard of care (SOC) tasks. **Results:** 80 subjects participated in the 2 studies, 47 HCPs and 33 NPCs. 6% of untrained HCPs and 8% of untrained NPCs failed to read the Instructions for Use and made use errors. 37% of NPCs and 0% of HCPs requested training before use. 13% of untrained HCPs failed to check the dose when using the device and made a number of use errors resulting in incomplete injection. After training, 100% of subjects safely disposed of the device. **Conclusions:** All subjects delivered a safe and effective injection after training. NPCs were more likely to request training than HCPs. Having a background of medical training does not improve use outcomes in this population.

Disclosure: Adam Shames receives contracted fees from Ipsen Biopharmaceuticals; Fabien Jeannerot and Susan Smith are employees of Ipsen Biopharmaceuticals.

P9

Physical Activities in Daily Life and Functional Capacity Compared to Disease Activity Control in Acromegalic Patients: Impact in Self-Reported Quality of Life

[1, 2]**Renata Aparecida Elias Dantas,** [1]**Lara Benigno Porto,** [1]**Juliano Coelho Oliveira Zakir, Gabriella Mendes Soares Motta,** [1]**Luciana Ansaneli Naves**

[1]Unit of Endocrinology- Faculty of Medicine, University of Brasilia, Brazil; [2]Faculty of Physical Education-UniCeub, Brasilia, Brazil

Background: There is a lack of data on the impact of treatment and hormonal control in daily life activities and self-reported quality of life in patients with acromegaly.

Objective: To evaluate the quality of life and its association with daily physical activity and disease control in acromegalic patients.

Methods: A cross sectional, case series study, composed of 42 patients recruited from the Neuroendocrinology Unit of the University Hospital of Brasilia. Level of physical activity was accessed by the International Physical Activity Questionnaire (IPAQ 6- short-form), which evaluates the weekly time spent on physical activity of moderate to vigorous intensity in different contexts of life. Quality of life was evaluated by The Medical Outcome Study Questionnaire Short Form (SF 36). Data was compared to GH and IGF-1 levels. Students' t test and Fisher test were used, p <0.05, SPSS 17.0.

Results: 22 women, aged 51.33 ± 14.33 and 20 men, aged 46.2 ±13.18 were evaluated. Arthralgia was present in 83% of cases. In men, the most common algic sites were Knees (73%), vertebral column (47% lumbar and 53% thoracic and cervical segments), hands and wrists (40%). Higher scores on SF-36 were observed in patients with intermediate or high levels of physical activity, in domains social functioning (75 CI 57.3-92.6), general health (75.5 CI 60.4-90.5), mental health (70 CI 57.8-82.1). **Conclusions:** In this study, the presence and severity of physical disability and pain were not associated to initial GH and IGF-1 levels or time of exposure to GH excess. However, the patients considered controlled, with normal a normal age-adjusted IGF-1, presented higher scores in SF-36, in physical and emotional domains, compared to patients with persistent hypersomatotrophism. These findings suggest benefits of metabolic control in self-reported quality of life.

Disclosure: The authors have no relationships to disclose.

P10

Presurgical Somatostatin Analogues Versus Direct Surgery in the Treatment of Newly Diagnosed Acromegalic Patients: A Systematic Review of Randomized Studies

Nunes VS[1], Correa JMS[1], Puga MES[2], Silva EMK[2], Boguszewski CL[3]

[1]Department of Internal Medicine, Botucatu Medical School, State University/UNESP, Sao Paulo, Brazil; [2]Brazilian Cochrane Centre - Discipline of Emergency Medicine and Evidence-Based Medicine, Federal University of Sao Paulo (UNIFESP), São Paulo, Brazil; [3]Department of Internal Medicine, Endocrine Division (SEMPR), Federal University of Parana, Curitiba, Brazil

Introduction: Previous studies addressing presurgical somatostatin anologues therapy in acromegaly patients have showed controversial results in surgical cure rates. **Objective:** We undertake a systematic review of randomized controlled trials that compared preoperative somatostatin analogue therapy with direct transsphenoidal surgery in the treatment of newly diagnosed acromegalic patients.

Methodology: The data sources were the following electronic database: Embase, Pubmed, Lilacs and Central Cochrane. The outcome measures included GH nadir after OGTT < 0, 4 (using sensitive assays) or < 1 µg/L (using RIA); random GH < 1 ng/mL (using sensitive assays) or < 2.5 ng/mL (using RIA); normal IGF-1 for age and gender; tumour shrinkage, duration of hospital stay, quality of life.

Results: 2100 references were identified and two reviewers (VSN and JMSC) independently screened the titles and abstracts to identify the studies. Twenty-one articles were potentially eligible for inclusion in the review: five were included and sixteen were excluded due to lack of randomization or because they were only controlled studies. A pool of 281 patients was randomly assigned to preoperative treatment with somatostatin anologues (lanreotide n = 90; octreotide n = 51) or to direct transsphenoidal surgery (n = 140). The analyses showed that in four studies (n = 261) the use of somatostatin analogues before transsphenoidal surgery either improved significantly the surgical cure rates in patients with macroadenoma or reduced tumor size and invasion. One study included patients with microadenoma. However, the effect was inconclusive due to small numbers of subjects. The homogeneous and similar clinical outcomes have been plotted in a meta-analysis. **Conclusion:** Preoperative somatostatin analogues treatment might improve surgical cure rate in newly diagnosed acromegalic patients with pituitary macroadenoma.

Disclosure: CL Boguszewski and VS Nunes receive consulting fees from Novartis and travel expenses from Ipsen; JMS Correa, MES Puga, and EMK Silva, have no relationships to disclose.

P11
Profile of Acromegalic Patients in Use of Pegvisomant in a Tertiary Hospital in Brazil

[1]José Ítalo Soares Mota, [1]Aruana Neves Salvador de Alcântara, [1]Leiliária Maia Lemos Macedo, [1]Silbere Silva do Amaral, [1]Tânia Maria Bulcão Lousada Ferraz, [2]Jackson Oliveira Gondim, [3]Antônio Gilson Aragão Junior, [4]Dalgimar Bezerra de Menezes, [4]Luciano Franco, [5]Fernanda Scheridan de Morais Bezerra

[1]Department of Endocrinology, Hospital Geral de Fortaleza, Brazil; [2]Department of Neurosurgery, Hospital Geral de Fortaleza, Brazil; [3]Department of Radiology, Hospital Geral de Fortaleza, Brazil; [4]Department of Pathology, Hospital Geral de Fortaleza, Brazil; [5]Department of Nursing, Hospital Geral de Fortaleza, Brazil

INTRODUCTION: Pegvisomant is an analog of human GH that acts as a potent GH receptor antagonist and has the potential to achieve biochemical control in acromegalic patients whose control cannot be achieved by conventional therapy.

OBJECTIVE: To analyze the results of five patients with active acromegaly after conventional therapy successfully treated with pegvisomant.

METHODS: We report five cases of patients with active acromegaly and in use of pegvisomant, followed by the department of endocrinology of the HGF, having as source medical records. Of the five patients (2 males and 3 females), the mean age was 37 years and 9 months, and all patients had macroadenoma. Of these, four underwent trans-sphenoidal surgery of the pituitary, two underwent radiotherapy and all were receiving drug treatment with somatostatin analogue (octreotide), and dopamine agonist (cabergoline). Despite the association of therapeutic modalities, patients remained resistant, with GH levels of 13.48 ± 21.45 ng/ml and IGF1 above the upper limit of normal 2.4 ± 0.6 times. Pegvisomant therapy was initiated with 10 mg SC daily for all patients.

RESULTS: The follow-up time was 13.2 ± 4 months. The Nadir of IGF-1 occurred within 6 months of treatment, when three patients achieved normal IGF1 levels for their age group. The other two patients had significant reduction of IGF-1 with the addition of pegvisomant. In both, the dose has not been scaled to 20 mg daily. No patient showed significant increase in tumor size of pituitary evidenced by MRI 6 months post-pegvisomant. Treatment was well tolerated in all patients. No patient had reactions at the injection site and only one had elevated liver enzymes in the first three months (TGO-160 u/l, TGP-63 u/l), with normalization in the following months.

CONCLUSION: Treatment with pegvisomant significantly improved serum levels of IGF-1 in the studied patients. Treatment was well tolerated and can be considered safe and effective in the period of monitoring.

Disclosure: The authors have no relationships to disclose.

P12
Successful Reversion of Cardiomyopathy Following Treatment with Somatostatin Analogs in a Patient with Acromegaly

Julieta Tkatch, Betiana Perez, Agustina Haun, Natalia García Basavilbaso, Mirtha Guitelman

Endocrinology Department, Durand Hospital, Buenos Aires, Argentina

Introduction: Cardiovascular complications are a major cause of morbidity and mortality in patients with acromegaly. GH hypersecretion appears to have a direct detrimental effect on the heart, but other cardiovascular risks factors such as hypertension and diabetes mellitus are often associated. Controlling GH hypersecretion can reverse some features of acromegalic cardiomyopathy such as myocardial hypertrophy and diastolic dysfunction particularly in patients younger than 45 yrs, and those with a short history of GH hypersecretion.

Case report: a 62 year old male patient was referred to our department for clinical suspicion of acromegaly due to typical features of GH excess. Two years before he had presented two episodes of paroxysmal supraventricular tachycardia, and 8 months later he was discovered to have a severe left ventricular dilated cardiomyopathy. He had history of Type II Diabetes and dyslipidemia. Diagnosis of acromegaly was made through IGF1 levels reaching values of 5,5 the UNL. Pituitary image revealed a 1 cm adenoma. A severe deterioration of the systolic function with left ventricular ejection fraction (LVEF) of 28% (normal value >55%) and a great dilatation of the Left Ventricle (LV), was reported by echocardiography. Due to the high cardiac risk medical treatment with Octreotide LAR 30mg/monthly was indicated. After nine months under somatostatin analogs clinical and biochemical parameters improved significantly: IGF1 decreased to 1,9 the UNL and the LVEF increased to 56%, a normal value, together with a normalization of the left ventricular size. **Conclusion:** Treatment of acromegaly seems to improve cardiac function in the short term and probably has an important effect on myocardial hypertrophy and ventricular dilation. We demonstrate the successful reversion of the cardiomyopathy in a male with acromegaly with severe cardiac deterioration after short-term somatostatin analogs treatment despite his age and the lack of IGF1 normalization.

Disclosure: The authors have no relationships to disclose.

P13
Transphenoidal Surgery for GH Pituitary Adenomas: An Anatomical Study

Locatelli M[x], Carrabba G[x], Rampini P[x], Mantovani G[x§], Spada A[x§]

[x]Neurosurgery, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano, [§]Endocrinology, Università degli Studi di, Milano, Italy

BACKGROUND: Transphenoidal surgery is an effective treatment for acromegalic patients with GH producing pituitary adenomas. Since acromegaly is a systemic disease which causes multiple bony alterations, we hypothesized that it could affect the sphenoid sinus anatomy. Aim of the study was to determine whether acromegalic patients have sphenoid sinus alterations with potential surgical impact.

METHODS: Forty-six consecutive patients (23 acromegalics - GH group, 23 non-acromegalics - nGH group) undergoing transphenoidal surgery were included in this study. Pre-operative volumetric CT scan of the head was used to assess the following anatomic characteristics: type of sphenoid sinus (sellar, pre-sellar, conchal); number of intrasphenoid septa; number of carotid-directed septa; intercarotid distance; depth of the sphenoid sinus; depth and size of the sella.

RESULTS: The sphenoid sinus was of the pre-sellar/conchal type in 26% of the patients with acromegaly (n=23) versus 9% of the patients of nGH group (n=23). The number of intrasphenoid septations was significantly higher in GH group than in nGH group (P= .03). Interestingly, the intercarotid distance was smaller in GH patients than in nGH displaying a trend toward significance (P= .05). The sphenoid bone was deeper in GH group as compared to nGH group (P= .01) but the distance sphenoid sinus-sella was reduced (P< .01). Finally, the sella was not deeper, nor larger in acromegalic patients.

CONCLUSIONS: The sphenoid sinus of acromegalic patients resulted deeper, characterized by more septa and by a reduced intercarotid distance. These alterations deserve special pre- and intraoperative care, being potentially responsible for surgical difficulties.

Disclosure: The authors have no relationships to disclose.

P14
Which is Better Test for Diagnosing Acromegaly in Patients with Co-Existing Diabetes Mellitus: GH, IGF-1 or IGFBP-3?

Pinaki Dutta[1], Saurabh Singhal[2], Naresh Sachdeva[1], Kanchan Mukherjee[3], Ashis Pathak[4]

[1]Endocrinology, Post Graduate Institute of Medical Education and Research, Chandigarh, India, [2]Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India, [3]Neurosurgery, Post Graduate Institute of Medical Education and Research, Chandigarh, India, 5Neurosurgery, Ward[4], Hull Royal Infirmary, United Kingdom

Purpose: Diagnosis of acromegaly in presence of uncontrolled diabetes mellitus is not well validated.

Method: The study included 10 patients of active acromegaly with uncontrolled blood glucose,10 patients of type 2 diabetes mellitus with poor glycemic control and 10 healthy subjects. The growth hormone level following oral glucose tolerance test and insulin - like growth factor-1(IGF-1) and insulin - like growth factor - binding protein -3 (IGFBP-3) were done at baseline in all the 3 groups and it was repeated after short term glycemic control in type 2 diabetics and acromegalics with diabetics.

Results: In the acromegalic group the basal GH value was very high (36.5 + 16.3) ng/ml and it was non-suppressible (32.5 + 14.3) ng/ml after OGTT. The mean IGF-1 and IGFBP-3 values were also high at baseline (208.38 + 38.51) ng/ml, and 7322 + 370 ng/ml respectively. In the non-acromegalic diabetic patients, the basal growth hormone value was marginally elevated (2.3 + 0.02) ng/ml. However, it was suppressible to 0.2 + 0.04 ng/ml after oral glucose load. In them the IGF-1 and IGFBP-3 values were not elevated and comparable to that of healthy controls. **Conclusions:** Basal serum GH and IGFBP-3 levels are not influenced by degree of glycemic control however serum IGF-1 levels should be interpreted with caution in patients of acromegaly with diabetes. Oral glucose load test has discriminating ability to diagnose acromegaly even with poorly controlled diabetes.

Disclosure: The authors have no relationships to disclose.

Appetite/Obesity

P15

Diencepephalic Syndrome Before Diagnosis of Childhood Craniopharyngioma – Results of Multinational Studies on 485 Long-Term Survivors After Childhood Craniopharyngioma

Hermann L. Müller[1*], Anthe S. Sterkenburg[1,2], Ursel Gebhardt[1], Anika Hoffmann[1]

[1]Dep. of Pediatrics, Klinikum Oldenburg; [2]University of Groningen, The Netherlands. [*]on behalf on the study committee of KRANIOPHARYNGEOM 2000/2007

Background: Hypothalamic involvement (HI) resulting in severe obesity is known to have major impact on quality of life in craniopharyngioma (CP) patients. HI is also associated with disturbances of satiety regulation leading to a failure to thrive and weight loss known as diencephalic syndrome (DS). The rate of DS and the outcome of CP patients with DS is unknown.

Methods: 485 CP patients have been recruited in HIT-ENDO and KRANIOPHARYNGEOM 2000/2007. 21 CP patients (4.3%) presented with a BMI<-2SD at diagnosis. In 4 of 21 cases low BMI could be explained by prematurity or congenital heart failure. 11 patients presented with DS due to proven hypothalamic involvement (HI). 3 patients presented without HI, in 3 patients HI was not evaluable. We compared weight development since birth at standardized time points (based on a German health survey) in CP presenting DS, normal weight or obesity (BMI>3SD) at the time of diagnosis. **Results:** Weight development during early childhood could be analyzed in 9 of 11 DS patients. Decreases in BMI (>-1SD) were detectable in 4 patients within the first year of life, in 2 patients in the second year of life, in 2 patients in the 5th year, one patient was already dystrophic at birth. Accordingly, 7 of 11 patients showed BMI reduction within the first two years of life. During follow-up, DS patients showed a significant postoperative weight gain comparable to patients who presented with normal weight at time of diagnosis resulting in obesity (median BMI +3.98SD) after 8-12 years.

Conclusion: DS is a rare clinical manifestation of CP. In the majority BMI SDS reduction becomes manifest in early childhood, in some cases changes in BMI SDS develop later, but years before other symptoms are obvious. Low BMI at time of diagnosis does not prevent weight gain in CP with DS.

Disclosure: The authors have no relationships to disclose.

P16

No Long-Term Weight Reduction After Gastric Banding (Lagb) in Obese Patients with Craniopharyngioma Involving Hypothalamic Structures – Experiences from Kraniopharyngeom 2000/2007

Anika Hoffmann[1], Anthe S. Sterkenburg[1,2], Ursel Gebhardt[1], Hermann L. Müller[1*]

*[1]Dep. of Pediatrics, Klinikum Oldenburg; [2]University of Groningen, The Netherlands. *on behalf on the study committee of KRANIOPHARYNGEOM 2000/2007*

Background: Craniopharyngiomas are embryogenic malformations which lead to eating disorders and morbid obesity due to hypothalamic involvement. The experience with laparoscopic adjustable gastric banding (LAGB) in obese craniopharyngioma patients is limited especially in regard to long-term effects and tolerability.

Patients and methods: We are reporting on four patients with childhood craniopharyngioma diagnosed at age 2, 13, 12, and 20 years.

Results: Body mass index (BMI-SDS) at diagnosis was -0.9, +4.5, +4.7 and +0.23 SD. All patients developed morbid obesity (BMI-SDS: +10,87, +10.36, +11.4, +6,2) so that 11, 5, 9 and 3 years after diagnosis LAGB were performed. LAGB were well tolerated. During long-term follow-up, the nadir BMI SDS (+6.9, +9.5, +7.8, +4.9) were reached 2.0, 0.5, 1.0, 0.8 years after LAGB. At last evaluation 9.1, 5.3, 7.1, 7.1 years after LAGB, the patients BMI (BMI SDS at last evaluation: +10.2, +13.9, +10.2, +6.3) had increased again but remained at a constant level comparable with baseline BMI SDS at the time of LABG. Quality of life was not decreased due to LAGB and tolerability was sufficient.

Conclusions: We conclude that LAGB is feasible and could have clinical relevant effects on long-term weight stabilization of obese craniopharyngioma patients with hypothalamic syndrome. However, a significant weight reduction was not achieved after LAGB in patients with childhood craniopharyngioma. Non-reversible bariatric procedures such as gastric bypass are not recommended for treatment of obese children and adolescents with craniopharyngioma due to ethical considerations.

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Cellular & Molecular

P17

cAMP Exerts Proliferative and Anti-proliferative Effects by Activating Both cAMP-dependent Protein Kinase A (PKA) and Exchange Proteins Directly Activated by cAMP (Epac) in Different Pituitary Cells Types

E.Vitali[1], E.Peverelli[2], G.Mantovani[2], G.Lasio[4]; P.Beck-Peccoz[2], A.G.Lania[1,3], A.Spada[2]

[1]Laboratory of Cellular and Molecular Endocrinology, IRCCS Clinical and Research Institute Humanitas, Rozzano; [2]Endocrine Unit, Department of Clinical Sciences and Community Health, Fondazione IRCCS Ospedale Maggiore Policlinico, University of Milan; [3]Endocrine Unit, IRCCS Humanitas Clinical Institute, Rozzano, BIOMETRA Dept, University of Milan, Neurosurgery Department, IRCCS Humanitas Clinical Institute, Rozzano, Italy

cAMP is implicated in the inhibition or stimulation of proliferation depending on cell type. As far as the pituitary is concerned, the activation of cAMP dependent pathways generates proliferative signals in GH-secreting adenomas whereas the action of cAMP on other pituitary cell types remain uncertain.

Moreover, although cAMP effects were initially attributed to protein kinase A (PKA) activation, two cAMP-activated guanine nucleotide exchange factors (Epac1, 2) have recently been identified as modulators of cAMP action.

Aim of the present study was to investigate the effects of cAMP on cell proliferation in different pituitary cell types and to identify the specific role of PKA and Epac in mediating these effects.

We tested the effects of different cAMP analogs (PKA-selective, Epac-selective or non selective) on cell proliferation, evaluating also the expression of cyclin D1/D3 and the cyclin dependent kinase inhibitor p27, in different pituitary adenomas (GH-, PRL-secreting or non secreting adenomas) and in appropriate cell lines (GH3, MMQ and HP75).

We found that non selective cAMP analog caused a 50% stimulation of somatotroph cells proliferation, whereas they exerted an opposite inhibitory effect on lactotrophs (-55%) and non-functioning (-58%) pituitary cells, these data being obtained also in the corresponding cell lines and confirmed by the expression of CD1, CD3, p27 proteins. Moreover, stimulatory and inhibitory effects induced by cAMP analog were mimicked by the PKA- and Epac-selective cAMP analogs.

In conclusion, we demonstrated that cAMP exerted opposite effects on the proliferation of different pituitary cell types, these effects being mediated by both PKA and Epac through the activation of different pathways, i.e. CREB and Rap1, respectively.

Disclosure: The authors have no relationships to disclose.

P18

mTOR Mediates IGF-1 Proliferative Effects in a Rat Pituitary GH/PRL Secreting Pituitary Adenoma Cell Line

Maria Chiara Zatelli[1,2], Mariaenrica Bellio[1], Teresa Gagliano[1], Ettore degli Uberti1,[2]

[1]Section of Endocrinology, Department of Medical Sciences, University of Ferrara, Ferrara, Italy
[2]Laboratorio in rete del Tecnopolo "Tecnologie delle terapie avanzate" (LTTA) of the University of Ferrara, Ferra, Italy

IGF-1 represents an important growth factor in pituitary physiology and pathology, also mediating the negative feed-back mechanisms on somatotroph axis. We previously demonstrated that IGF-1 promotes cell viability in primary cultures of human non functioning pituitary adenomas, by a mechanisms involving, at least in part, mTOR signaling, which is involved in many pathways controlling proliferation. We aimed at investigating whether mTOR may mediate IGF-1 effects also in an in vitro model of GH/PRL secreting pituitary adenoma, the rat GH3 cells. Therefore, GH3 cells were incubated in the presence or in the absence of 100 nM IGF-1 with either Everolimus, an mTOR inhibitor, or NVP-BEZ235, a PI3K/mTOR inhibitor at concentrations ranging from 10 to 500 nM for 72 h. We found that Everolimus significantly inhibits cell viability at concentrations as low as 25 nM, with a cell viability reduction of 50% ($P<0.01$). The lowest NVP-BEZ235 concentration that significantly inhibits cell viability is 50 nM, with a cell viability reduction of 40% ($P<0.01$). In addition, IGF-1 significantly ($P<0.05$) increased GH3 cell viability by 20-60% at concentrations ranging from 10 to 500 nM, independently of the concentration. These proliferative effects were completely abrogated by co-incubation with 50-100 nM Everolimus or NVP-BEZ235. On the other hand, 50 -100 nM Everolimus or NVP-BEZ235 significantly promoted caspase 3/7 activity (15-25%; $P<0.02$). Basal apoptotic rate was not significantly influenced by IGF-1, which did not protect GH3 cells from the pro-apoptotic effects of Everolimus and of NVP-BEZ235. These results confirm that IGF-1 has proliferative effects on pituitary adenoma cells, which are mediated, at least in part by mTOR. On the contrary, IGF-1 does not prevent the pro-apoptotic effects induced by mTOR inhibitors.

Disclosure: The authors have no relationships to disclose.

CRH/ACTH/Cushing

P19

Development of an Algorithm to Identify Cushing Disease Patients in a US Administrative Claims Database

Burton T[1], Gomez Rey G[1], Neary M[2], Ludlam W[2], Le Nestour E[3]

[1]OptumInsight; [2]Novartis Pharmaceuticals Corporation; [3] inVentiv Health Clinical

Objective: Using administrative claims from a large US health plan, develop an algorithm to identify Cushing disease (CD) patients, a condition not uniquely identified in ICD-9 disease classification system.

Methods: Standardized disease and procedure codes were used to identify CD patients in a claims database. Without a specific CD diagnosis code, the algorithm began with an ICD-9 diagnosis code (255.0) for Cushing Syndrome (CS), a broad spectrum of etiologies encompassing CD. Medical experts evaluated 18 pituitary conditions and procedures to distinguish CD from CS. Baseline characteristics of selected patients were summarized.

Results: Of 4 million health plan enrollees with medical and pharmacy benefits, 9,994 had evidence of 1+ CS diagnosis codes between 1/1/2007–12/31/2011, of which 1,467 (15%) also had evidence of 1+ of the following conditions: benign pituitary neoplasm: 476 (32% of 1,467); pituitary disorders such as hyperfunction and hypothalamic control: 966 (66%); hypophysectomy: 307 (21%); cranial stereotactic radiosurgery: 68 (5%); bilateral inferior petrosal sinus hormone sampling: 48 (3%). Among patients identified by this algorithm, 76% were female, mean(SD) age was 42(14) years, and 44% had evidence of a CD-related condition or procedure prior to their first CS diagnosis code.

Conclusions: The sex and age distribution of the selected population matched the known epidemiology of CD. Also nearly half the sample had a CD-related condition or procedure prior to their first CS diagnosis code, which suggests a delayed diagnosis cohort may exist. Early detection and treatment of CD may improve health outcomes, which we plan to examine further in the claims. Although challenging without unique diagnosis codes, CD cases may be identified using an algorithm and validated using medical records data. In addition to offering information about patients' healthcare experiences over time, administrative claims offer large, diverse patient populations, which for rare disease studies would not be possible otherwise.

Disclosure: The authors have no relationships to disclose.

P20

Different Cut-Off Values of the Insulin Tolerance Test, the High Dose Short Synacthen Test (250 μg) and the Low Dose Short Synacthen Test (1 μg) in Assessing Adrenal Insufficiency

Kyong Yeun Jung[1], Tae Hyuk Kim[1], Ahreum Khang[1], Jung Hee Kim[1], Kyung Won Kim[1], Hwa Young Cho[2], Sang Wan Kim[1], Seong Woon Kim[3], Seong Yeon Kim[1]

[1]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea, [2]Department of Internal Medicine, The Armed Forces Capital Hospital, Seongnam, Republic of Korea, [3]Department of Internal medicine, Kyunghee University College of Medicine, Seoul, Republic of Korea

The short synacthen test (SST) is widely used as alternative test to the insulin tolerance test (ITT) to investigate central adrenal insufficiency (CAI), but the methodology and cut-off values of the SST are controversial. We aimed to evaluate different cut-off values of the high-dose SST (250 μg, HDT) and the low-dose SST (1 μg, LDT) based on re-established cut-off value from the ITT in subjects with suspected CAI. We conducted ITTs in 208 normal subjects to establish the cut-off value for the ITT, and 28 of those subjects underwent the HDT and LDT. From 1999 to 2007, 182 patients with suspected CAI were recruited. ITTs, HDTs and LDTs were carried out in all patients. We assessed the optimal cut-off values of the HDT and LDT based on the re-established cut off value from the ITT. The 95th percentile of the peak cortisol level during the ITT in the normal control subjects was 14.9 μg/dl, which was considered a normal cut-off value. Receiver-operator characteristics (ROC) analysis revealed that the optimal cut-off values of peak cortisol in the LDT and HDT in patients with suspected CAI were 15.8 and 17.4 μg/dl, respectively. However, the cut-off values from normative data (mean-2SD) were 18.3 μg/dl for the LDT and 20.5 μg/dl for the HDT in normal control. The optimal cut-off values of SSTs needed to be individualized according to the type of SST and tested patient population. We suggested different cut-off levels: 15 μg/dl for the ITT, 18 μg/dl for the LDT and 20 μg/dl for the HDT in normal control, 16 μg/dl for the LDT, 17 or 18 μg/dl for the HDT in pituitary control.

Disclosure: The authors have no relationships to disclose.

P21
From Anorexia Nervosa to Nelson Syndrome: An Atypical Presentation of a Cushing's Disease

Boguszewski CL[1], Borba LA[2], Casagrande A[3], Czepielewski M[3], Boguszewski MCS[1]

Endocrine Division (SEMPR)[1] and Neurosurgery Division[2], Federal University of Parana, Curitiba, Brazil; Endocrine Division, Federal University of Rio Grande do Sul, Porto Alegre, Brazil[3]

A 14 year-old girl was initially evaluated in 2006 due to progressive decrease in weight associated with anorexia, vomiting, hair loss and secondary amenorrhea. At this time, she was diagnosed with anorexia nervosa according to the DSM criteria and a nutritional-psychologic therapy was started. One year later, she had gained 10 kg and rapidly developed symptoms and signs of hypercortisolism: central obesity, hypertension, facial plethora, muscle weakness, hirsutism and violaceous striae. Laboratorial evaluation confirmed the presence of an ACTH-dependent Cushing's syndrome, with a normal pituitary MRI and an IPSS indicative of Cushing's disease. She was subjected to a transsphenoidal surgery in May/2008, and a pituitary microadenoma was removed; immunohistochemistry ACTH ++/3, GH +/3, and Ki67 1-2%. Clinical and laboratorial hypercortisolism persisted and a medical therapy with ketoconazole was initiated in progressive doses up to 800 mg/day, with a partial response. After 6 months, cabergoline was added, but no further improvement was noted. Her clinical and laboratorial findings rapidly worsened and a bilateral adrenalectomy was carried out in June/2009, followed by replacement therapy with gluco- and mineralocorticoids. Her plasma ACTH levels increased progressively from 145 pg/mL in the first month after surgery to > 1250 pg/mL 18 months later. Clinically, only a mild hyperpigmentation in the skinfolds of her hands and feet was observed. At this moment, a MRI showed an intrasselar pituitary adenoma measuring 11x9x7 mm, extending to the right cavernous sinus. A second transsphenoidal surgery was performed in January/2011, without a complete resection of the tumor. Cabergoline was restarted and titrated to 1.5 mg/week, and after 12 months of treatment, there was a total regression of the tumor, which was not detected in the imaging. This case highlights many diagnostic and therapeutic pitfalls in an atypical case of Cushing's disease and the therapeutic effectiveness of cabergoline in Nelson's syndrome.

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P22
Late Night Salivary Cortisol (LNSF) Versus 24-H Urinary Free Cortisol (UFC) in the Diagnosis of Cushing's Syndrome (CS): A Concomitant Samples Collection Study During Three Consecutive Days

Paula C. L. Elias; Bruno F. C. Barone; Livia M. Mermejo; Margaret de Castro; Ayrton C. Moreira

Division of Endocrinology – Department of Internal Medicine - School of Medicine of Ribeirão Preto – University of São Paulo – Ribeirão Preto, Brazil

To evaluate the diagnostic performance of LNSF compared to UFC, we studied 75 patients referred for evaluation of CS. 43 patients had Cushing´s disease (CD) (38F/5M; 31.5±11.7y), 14 patients had adrenal CS (aCS) (14F; 35.3±16.4y) and 18 patients had primary obesity (OB) (17F/1M; age 38.2±13.6y). OB patients had LNSF and salivary cortisol post 1mg dexamethasone suppression test values within normal ranges (<350ng/dL and <150ng/dL, respectively). All CS diagnoses were confirmed by histology. Ethical Committee approved the study. On three consecutive days 24-h UFC were collected concomitantly with LNSF samples at 2300h. LNSF measurements were performed by RIA. UFC was measured by LC-MS/MS (0.3-43.0mg/24h). Data are expressed as mean±SD. Kruskal-Wallis ANOVA was performed as appropriated. Receiver-operating characteristic (ROC) curves were calculated. Significance was assumed when $P<0.05$. LNSF levels were higher in CD (2661±2169ng/dl) and aCS (1634±1385ng/dl) compared to OB patients (268±410ng/dl; $P<0.001$). UFC was higher in CD (362±1022μg/24h) and aCS (209±249μg/24h) compared to OB patients (21.0±22.6μg/24h, $P<0.001$). A positive correlation was found between LNSF and UFC in CD and aCS patients, $r=0.39$ and $r=0.84$, $P<0.0001$, respectively; but not in OB patients. ROC area under the curve for LNSF was higher compared to UFC (0.97vs0.92). Sensitivity and specificity were 86.8 and 96.9% for LNSF (cutoff: 350ng/dL) with a likelihood ratio of 14.2; and 91.5 and 78.8% for UFC (cutoff: 43ng/24h) with a likelihood ratio of 4.3. Considering all three samples, LNSF was diagnostic in all but one CD patients. However, UFC failed diagnosis in 6/43 (14%). In aCS, 3/14 (21.5%) LNSF and 6/14 (43%) UFC tests failed diagnosis. In OB patients false positive results in 1 or 2 samples was seen in LNSF tests (5/18; 27.8%) and in UFC (4/18; 22.2%). In conclusion, this study indicates the best performance of LNSF compared to UFC for CS screening considering its diagnostic accuracy and convenience.

Disclosure: The authors have no relationships to disclose.

P23

Symptomatic Perioperative Venous Thromboembolic Events in Patients with Cushing's Disease: A Call For Prophylaxis

Jessica Brzana, Chris Yedinak, Shirley McCartney, and Maria Fleseriu

Northwest OHSU Pituitary Center, OHSU School of Medicine, Departments of Medicine and Neurological Surgery, Portland, Oregon, USA

Introduction: Cushing's syndrome (CS) is often associated with hemostatic alterations combined with a prothrombotic phenotype and gender predisposition. The risk of perioperative atherothrombotic and venous thromboembolic events (VTEs) in CS patients are reportedly 10-fold compared with the general population and compounded by other known perioperative thrombotic risks.

Objective: To determine the perioperative incidence of symptomatic VTEs in Cushing's disease (CD) patients at a single site.

Method: We conducted a retrospective chart review of 87 consecutive patients who underwent surgical resection with pathology confirmed CD (2004 -2011). Symptomatic VTEs were confirmed by US Doppler and/or CT.

Results: VTEs occurred in 10 (4M/6F; 11%) patients: 8 (80%) deep vein thrombosis, 4 (40%) pulmonary embolism, and 2 (20%) cerebrovascular thrombosis. Mean age, BMI, CD duration, and time from surgery to VTE were: 46±13yrs, 33.2±6.3, 4.4±3.9 yrs, and 0.71±0.6 mos, respectively. Postoperatively, 5 patients in remission, 5 persistent hypercortisolism. No deaths recorded.

Discussion: Despite limitations inherent to retrospective review, we confirm a high (11%) perioperative incidence of VTEs in the absence of thromboprophylaxis. Though various abnormalities of coagulation and fibrinolysis have been reported, their causal relationship with the onset of clinically overt thrombosis or their predictive role still remains to be confirmed. CD patients are at higher risk of perioperative VTEs, similar to non-prophylaxis abdominal/pelvic surgery patients (14.3%). One CS study showed prophylaxis could decrease VTE complications from 20% to 6.0%. Appropriate thromboprophylaxis has a desirable risk/benefit ratio and is cost effective. However, postoperative anticoagulation or VTE prophylaxis is not routinely administered in CD patients.

Conclusion: Increased awareness of VTEs in CD/CS patients is highly desirable. A decision regarding antithrombotic prophylaxis should be based on clinical risk factors and results of coagulation studies. Further prospective investigations are required to optimize anticoagulant protocols (dosing and duration) along with individualized assessments of VTE and bleeding risk.

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Growth Hormone Deficiency

P24

iSYS Versus Immulite: A Clinical Comparison of Assay Specific Cut-Offs for the Insulin Tolerance and Pyridostigmin GHRH Test

[1]Klose, M, [2]Frystyk, J, [3]Andersen M, [4]Laurberg P, [2]Christiansen JS and [1]Feldt-Rasmussen U

[1]Department of Medical Endocrinology Copenhagen University Hospital, Rigshospitalet; [2]Department of Internal Medicine and Endocrinology Aarhus University Hospital; [3]Department of Medical Endocrinology Odense University Hospital; 4Department of Medical Endocrinology Aalborg University Hospital, Denmark

Background: It is well recognized that the currently available GH assays yield different results. To minimize this inter-assay variability, new criteria for the standardization and evaluation of GH-assays have recently been established. One new commercial assay, the iSYS GH-assay from Immunodiagnostic Systems, fulfill the novel criteria and has been reported to yield lower GH concentrations than the widely used Siemens Immulite 2000 assay.

Aim: To perform a head-to-head comparison of the iSYS and Immulite 2000 GH-assays and establish assay and test specific cut-offs for the insulin tolerance test (ITT) and pyridostigmin (PD)-GHRH test.

Methods: Plasma samples from 90 healthy controls and 439 patients protocolled for evaluation of posttraumatic hypopituitarism, collected during ITT or PD-GHRH, were analyzed by the two assays. First, we measured the full time profiles with the Immulite assay; secondly, all peak values were re-evaluated by the iSYS assay. GH peak concentrations measured by the two assays were compared, and test and assay specific cut-offs defined by the lower 2.5th percentile from healthy controls calculated.

Results: The correlation between methods was high in both healthy controls (iSYS = 0.42 + 0.93xImmulite; r2=0.96), and patients (iSYS = 0.40 + 0.96xImmulite; r2=0.95), with no systematic difference between the assays. The cut-off for the ITT was 2.6µg/l (iSYS) and 2.7µg/l (Immulite), respectively. The cut-off for the PD-GHRH test was BMI dependent, and defined at a peak GH of 10.4µg/L (iSYS) vs. 11.4µg/L (Immulite) at BMI < 25 kg/m2, at a peak GH of 3.6µg/L (iSYS) vs. 4.0µg/L (Immulite) at BMI 25-30 kg/m2, and a peak GH of 2.5µg/L (iSYS) vs. 2.5µg/L (Immulite) at BMI > 30 kg/m2. Conclusion: The two methods were highly correlated, with no systematic difference. We did thus not retrieve lower concentrations measured by iSYS as compared to Immulite, and accordingly, very similar cut-offs from healthy controls were described.

Disclosure: The authors have no relationships to disclose.

Growth Hormone

P25

Effects of an Amino Acid Based hGH Secretagogue on Triiodothyronine

Heaton AL[†], Tam CS[‡], Rood J[‡], Gupta A[‡], Greenway FL[‡]

[†]Sierra Research Group, Salt Lake City, Utah, [‡]Pennington Biomedical Research Center, LSU System, Baton Rouge, Louisiana, USA

Background: In a recent randomized, double-blind, cross-over clinical trial, serum growth hormone (hGH) increased 682% above baseline 120 minutes after oral administration of an amino acid-based dietary supplement (SeroVital™), p=0.01 vs. placebo. In contrast to the mechanism of hGH stimulation by ghrelin, we hypothesize that the supplement suppresses somatostatin, a known inhibitor of both hGH and TSH. To test this hypothesis, we measured triiodothyronine (T3) after administration of the amino acid-based supplement.

Methods: Sixteen healthy subjects [12 males, 4 females; mean age= 32±14 years; BMI=26.4±5.0 kg/m2] participated in a double-blind, placebo-controlled, cross-over trial. After an overnight fast, T3 concentrations were measured at baseline and 120 minutes after consuming the placebo or the amino acid-based supplement. Differences were compared to baseline by independent t-tests and to each other by paired t-tests. Statistical significance was set at $p<0.05$.

Results: After placebo administration, T3 concentrations significantly dropped by 6.10±8.5ng/dL (mean±SD) (106ng/dL at time 0 to 100ng/dL at 120 minutes, p=0.01). This decrease was expected due to the normal circadian drop of T3 during the morning hours. However, after administration of the amino acid supplement, the magnitude of the T3 drop was blunted by nearly 50%, 3.3±0.7ng/dL (101ng/dL at time 0 to 97.3ng/dL at 120 minutes, NS), whereas the final T3 concentration was not significantly reduced from baseline. There was no difference in the T3 reduction between the supplement and placebo conditions, 2.8±11.8ng/dL (p=NS).

Conclusions: Maintenance of triiodothyronine levels by the amino acid-based supplement but not by the placebo adds support to the hypothesis that somatostatin inhibition may be responsible for the observed increase in hGH by SeroVital™ in healthy men and women. This mechanism is in contrast to ghrelin mimetics for increasing hGH, which are associated with increased hunger. The direct support of T3 may provide additional metabolic advantages, an outcome to be investigated in subsequent studies.

Disclosure: Amy Heaton is an employee of Sierra Research LLC; Frank Greenway is a consultant for Basic Research, Citius Pharmaceutical, Esia Pharmaceutical, General Nutrition Corporation, Japan Tobacco Pharmaceutical Division, Lithera Inc., Thetis Pharmaceuticals and Unigene Labs, on the Editorial Board of Diabetic Living, on the Medical Advisory Board of Jenny Craig, on the Advisory Board of Pam Labs and Zafgen, on the Scientific Advisory Board of Novo-Nordisk and Orexigen, has patents licensed and stock with Neuro-Quest, stock options with NuMe Health and Plensat, and stock with Origin Biomed; Alok Gupta, Jennifer Rood, and Charmaine Tan have no relationships to disclose.

P26

Estrogen Regulates Exercise-Induced Pituitary Type 1 Deiodinase Increase and Growth Hormone Secretion

[1]Ignacio DL, [2]Silvestre D, [2]Cavalcanti-de-Albuquerque JP, [2]Louzada R, [1]Frankenfeld TGP; [2]Werneck-de-Castro JPS, [1]Carvalho DP

[1]LFEDR & [2]LBE, UFRJ, RJ, Brasil

Background: Acute aerobic exercise is a potent stimulus to growth hormone (GH) release, pituitary type 1 deiodinase (D1) is also stimulated by exercise and triiodotironine (T3) positively acts on GH synthesis. Little is known about the relationship between changes of pituitary D1 and GH secretion after exercise.

Objective: We aimed to study the effect of female gonadal steroids and D1 activity on post-exercise GH secretion.

Methods: Female Wistar rats were divided into: sham-operated sedentary (ShS), ovariectomized sedentary (OxS), sham-operated submitted to exercise (ShEx) and ovariectomized submitted to exercise (OxEx). ShEx and OxEx were submitted to 20 minutes treadmill acute exercise at 75% of maximum velocity. The animals were killed by decapitation 10 days after ovariectomy, immediately after the exercise and during the recuperation period (30 minutes). Pituitary was dissected out and D1 activity was measured. Total serum GH was determined by radioimmunoassay.

Results: Pituitary D1 activity increased just after exercise in ShEx (51%), and serum GH levels increased 30 min after exercise in the same group (23,5 ± 5,7ng/ml) compared to baseline (8,9 ± 2,8ng/ml). Both responses were blunted in ovariectomized rats.

Conclusions: Acute exercise positively regulates pituitary D1 activity and GH secretion, and both effects depend on intact gonadal function. We thus hypothesize the existence of a physiological relationship between pituitary D1 increase and GH secretion.

Disclosure: The authors have no relationships to disclose.

Miscellaneous

P27

Acute Effect of Increasing Glucocorticoid Replacement Dose on Insulin Sensitivity and Cardiovascular Risk in Patients with Adrenocorticotrophin Deficiency

Petersons CJ[1,2], Mangelsdorf BL[1], Thompson CH[2,3], Burt MG[1,2]

[1]Southern Adelaide Diabetes and Endocrine Services, Repatriation General Hospital, Adelaide, Australia; [2]Faculty of Health Sciences, Flinders University, Adelaide, Australia; [3]Discipline of Medicine, University of Adelaide, Adelaide, Australia

Adrenocorticotrophin (ACTH)-deficient patients taking ≥30 mg hydrocortisone/day have increased cardiovascular mortality. The mechanisms underlying this are unclear. Glucocorticoid excess causes insulin resistance and postprandial hyperglycemia, which are independent cardiovascular risk factors. Resistance to insulin's cardiovascular effects, especially postprandially, may underlie this association. The aim was to determine whether increasing hydrocortisone to 30 mg/day in ACTH-deficient patients reduced insulin sensitivity, and consequently, by attenuating insulin's hemodynamic effects, increased cardiovascular risk.

Seventeen ACTH-deficient subjects, usually taking ≤20 (17±3) mg/day hydrocortisone, were studied before and after increasing hydrocortisone to 30 mg/day for 7 days. Insulin sensitivity was estimated by the Matsuda Index, calculated from a frequently-sampled 75g oral glucose tolerance test. Cardiovascular function was assessed pre- and post-glucose load. Measures of arterial stiffness (augmentation index (AIx) and pulse wave velocity (PWV)) were estimated by pulse wave analysis. Reactive hyperemia index (RHI), a marker of endothelial function, was quantified by peripheral arterial tonometry. Data were analyzed using paired t-tests. Our Institution's ethics committee approved the study.

There were no significant changes in fasting (86.2±2.7 vs 88.0±3.1 mg/dL, p=0.23) or 2-hour (150.4±11.7 vs 148.1±14.2 mg/dL, p=0.79) glucose concentration, nor the Matsuda Index (9.4±3.4 vs 7.1±1.4, p=0.32), on the higher glucocorticoid dose. Fasting AIx (24.9±2.7 vs 22.6±2.6 %, p=0.04) and RHI (2.3±0.2 vs 2.0±0.2, p=0.04) were lower, and fasting PWV unchanged (9.4±1.0 vs 9.1±0.9 m/sec, p=0.24), on the higher glucocorticoid dose. There were no significant differences in post-glucose load change in AIx, PWV or RHI on the higher glucocorticoid dose.

In summary, increasing hydrocortisone to 30mg/day did not alter insulin sensitivity and exerted variable effects on cardiovascular risk markers, reducing endothelial function but also a measure of arterial stiffness. We conclude that endothelial dysfunction contributes to the increased cardiovascular mortality with higher glucocorticoid doses. This is likely a direct glucocorticoid effect, not mediated by insulin resistance.

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Disclosure: The authors have no relationships to disclose.

Pituitary Function

P28
A Case of Idiopathic Hypothalamic Failure?

VB Crawford, MS Elston, JV Conaglen

Departments of Endocrinology, Waikato Hospital, Hamilton, New Zealand

A 38 year old female librarian presented acutely with bradycardia (30-34bpm), hypothermia (T30°C), and confusion. Investigations revealed hyponatremia (sodium 126mmol/L), secondary hypothyroidism, hypogonadism, and an inadequate cortisol response to illness (cortisol 450nmol/L). No precipitating factors were identified. She was rewarmed and given hydrocortisone and thyroid hormone replacement.

Over the preceding 18 months, asymptomatic hypernatremia (sodium 149-154mmol/L) with no polyuria or polydipsia. She had a neuroblastoma treated at age four by resection, chemotherapy but not radiation. She had a six-month history of amenorrhea on a background of oligomenorrhoea since menarche. She denied sleep disturbance, hyperphagia, cognitive or emotional disturbance. She had no history of exposures e.g. toluene or nutritional deficiency. There was no personal or family history of autoimmune disease, porphyria or infiltrative disorders.

Examination revealed no features of systemic disease. Her height was 153cm, BMI 38.4 m/kg^2.

Magnetic resonance imaging (MRI) was unremarkable. 24hr urinary volume was 3.28L/day. Water deprivation testing showed elevated urinary and plasma osmolality (781mosmol/kg and 316mosmol/kg respectively), but no symptoms of thirst. Insulin-induced hypoglycemia was consistent with partial ACTH and severe GH deficiencies. Serum and cerebrospinal fluid tumor markers were normal.

She was advised to closely monitor her temperature with a low-reading thermometer and maintain a rigid schedule of fluid intake. At 18 months follow up MRI and tumor markers have remained unchanged. No new hypothalamic symptoms have developed and there is no evidence of recurrent neuroblastoma.

Discussion

Our patient had progressive hypothalamic failure with loss of pituitary function, thirst and temperature regulation with no cause identified after 18 months follow-up. Adult-onset hypothalamic dysfunction may result from a variety of causes including tumors, infiltrative disorders, radiation damage and infectious causes. Neuroblastoma has been postulated to be a rare paraneoplastic cause of hypothalamic dysfunction (1) but it appears unlikely to be related in this case.

References: 1. Sirvent et al. Medical pediatric oncology 2002; 40:326-8.

Disclosure: The authors have no relationships to disclose.

P29
Clinical Characteristics of 15 Patients with Hypophysitis

Toko Muraoka, Izumi Fukuda, Naomi Hizuka and Atsuhiro Ichihara

Department of Medicine II, Tokyo Women's Medical University, Tokyo, Japan

Background: Hypophysitis is a rare chronic inflammatory disease that causes hypopituitarism. Although pituitary biopsy is informative for confirming a pathogenesis of hypophysitis, it is not always easy to perform due to invasive procedure.

Objective: In this study, we investigated characteristics of clinical presentation and endocrinological and MRI findings in patients with hypophysitis due to various etiologies.

Patients and Methods: We studied 15 patients (M/F 6/9, aged 29-76 years old) who were admitted to our hospital between 2010 and 2011. Clinical symptoms, pituitary functions, MRI findings and pathogenesis of hypophysitis in each patient were investigated using medical records.

Results: The most common first symptoms were general fatigue and headache. Four patients had polyuria, and two patients were diagnosed incidentally during examinations for other diseases. Pituitary function tests revealed that deficiencies of GH, gonadotropin, TSH and ACTH were observed in 9 (60%), 9 (60%), 8 (53%) and 6 (40%) patients, respectively. Eight (53%) patients had diabetes insipidus. Hypertrophic dura were observed in 9 (60%) patients by MR imaging. Eventually, 7, 3 and 5 patients were diagnosed as adenohypophysitis (AH), infundiblo-neurohypophysitis (INH) and panhypophysitis (PH), respectively. Causes of hypophysitis were lymphocytic (n=7: AH 4, INH 1, PH 2), IgG4-related (n=2: INH 1, PH 1), Rathke's cleft cyst (n=2: AH), MPO-ANCA related (n=1, INH), pachymeningitis, systemic lupus erythematosus and right orbital abscess (n=1, each, PH).

Conclusion: Clinical features of hypophysitis varied widely and there were no specific findings to each pathogenesis of hypophysitis. Hypertrophic dura was observed in 60% of the patients by MRI, and this finding may be helpful for a prediction of inflammatory change of pituitary region and its surroundings.

Disclosure: The authors have no relationships to disclose.

P30
Comparıson of Low Dose ACTH and Glucagon Stimulatıon Tests with Insulin Tolerance Test

Simsek, Y; Tanriverdi, F; Diri, H; Karaca, Z; Unlühizarci, K; Arıbas, S; Kelestimur, F

Department of Endocrinology, Erciyes University Medical School, Kayseri, Turkey

Introduction: The insulin tolerance test (ITT) has been considered as the gold standard test for evaluating the hypothalamic-pituitary-adrenal (HPA) and growth hormone (GH) axes. We aimed to compare ITT, glucagon stimulation test (GST) and low dose ACTH test in patients with pituitary disorders in this study.

Material and Method: One hundred-ten patients were included in the study. To assess growth hormone (GH) – insulin like growth factor (IGF-1) axis, GST, and ITT were performed. 1 μg ACTH stimulation test was used in addition to GST and ITT, for assessing hypothalamic-pituitary-adrenal (HPA) axis.

Results: When HPA axis was evaluated; 76, 23.5 and 23.5 % of patients had insufficient cortisol responses to ITT, GST and low dose ACTH test respectively. Concordance of low dose ACTH stimulation and GST was found to be 72.7%. However, concordance of three tests (GST, ITT, and low dose ACTH stimulation) was only 20% in the evaluation of HPA axis. If a patient had sufficient cortisol response to ITT, cortisol response to GST and ACTH test were also found to be sufficient. On the other hand, if a patient had insufficient cortisol response to ITT, cortisol response to GST and ACTH test were found to be variable for HPA axis. When GH-IGF-1 axis was evaluated; 79.8 and 49.5% of patients had insufficient GH responses to ITT and GST respectively. Concordance of the ITT and GST was 72.4% in the evaluation of GH-IGF-1 axis.

Conclusion: In conclusion, cortisol responses to GST and low dose ACTH stimulation test are more concordant with each other than with ITT. Although glucagon and low dose ACTH are usually considered to be weaker stimuli than hypoglycemia, the present results are against.

Disclosure: The authors have no relationships to disclose.

P31
Endocrinologic Function in Nonfunctioning Pituitary Adenomas With Predominantly Exophytic Growth

Mika Habu[1], Shingo Fujio[1], Shunji Yunoue[1], Hiroshi Tokimura1,Usui Satoshi[2], Yasuyuki Kinoshita[2], Atsushi Tominaga[2], Kazunori Arita[1]

[1]Department of Neurosurgery, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan;
[2]Department of Neurosurgery, Graduate School of Biomedical Science Hiroshima University, Hiroshima, Japan

Introduction: We've surgically treated over 300 cases of non-functioning pituitary adenoma in a last decade. On MRI, pituitary glands were compressed thin by adenomas and surrounding the tumors. We found cases in which pituitary glands were not disfigured nor thinned and the adenoma mainly grew out of pituitary gland (Exophytic adenoma). We assessed pituitary function in these cases.

Material and Methods: The subjects are 14 patients, 4 males and 10 females with large nonfunctioning pituitary adenoma in which adenoma predominantly showed exophytic growth. Patients' age of the control ranged from 28 to 79 with mean of 47.18±14.68 (SD). The greatest diameter of the tumor ranged 23-46mm with mean of 35.64±6.4mm (SD). We assessed pre- and postoperative pituitary function of these cases. For control, the pituitary function of recent 67 consecutive cases, 30 male and 37 females, with nonfunctioning pituitary adenomas (NFoma) were also assessed. Patients' age of the control ranged from 19 to 84 with mean of 52±14.8 (SD). The greatest diameter of the tumor ranged 14 to 47mm with mean 28±10.5 mm (SD). Pituitary function was evaluated with pituitary provocation tests including insulin tolerance test in all patients.

Results: The peak values of the hormones in the pituitary function of the 14 subjects subjects to the preoperative stimulation tests were as follows: GH 13.79±5.46μg/L, cortisol 22.9±4.12 μg/dl. In control group, the peak values of the hormones to the preoperative stimulation tests were as follows: GH6 μg/L , cortisol 21 μg/dl. Especially in the 17 large tumors out of 67 controls whose diameters were > 30mm (36±5.3mm, 30-47mm), the GH and cortisol function were severely damaged: peak GH 1±1.22μg/L, peak cortisol 15±8.1 μg/dl. The GH and cortisol secretory function in patients of NFomas with exophytic growth were significantly preserved compared to patients with size-matched nonfunctioning adenomas ($p<0.05$): peak GH 13.79±5.46μg/L vs 1±1.22μg/L, peak cortisol 22.9±4.12 μg/dl vs. 15±8.1 μg/dl.

Conclusions: In some non-functioning pituitary adenomas, pituitary gland were not stretched thin and kept their normal configuration despite the largeness of tumor sizes. In these cases, the tumor showed mainly exophytic growth from the pituitary gland. Good preservation of secretory function of pituitary hormones including GH was outstanding characteristics of this subset of NFomas.

Disclosure: The authors have no relationships to disclose.

P32

Evaluation of Postoperative Day 1 and 5 Morning Serum Cortisol After Transsphenoidal Resection of Pituitary Adenoma to Predict Hypothalamic-Pituitary-Adrenal Function

Ivania M. Rizo[1], Joseph H. Miller[2], Bonita Agee[2], Kristen O. Riley[2] and T. Brooks Vaughan III[1]

[1]Department of Medicine, Division Endocrinology, Diabetes & Metabolism, University of Alabama at Birmingham; [2]Division of Neurosurgery, University of Alabama at Birmingham, Birmingham, Alabama, USA

INTRODUCTION: Controversy exists regarding the optimal assessment of the hypothalamus-pituitary-adrenal (HPA) axis in the early postoperative period after transsphenoidal surgery (TSS) for pituitary adenoma. We retrospectively examined the role of morning total serum cortisol level on postoperative day 1 (POD1) and postoperative day 5 (POD5) as predictors of long-term HPA function.

METHODS: Sixty-seven out of one hundred and eighty three patients who underwent TSS for pituitary adenoma between 2007 and 2012 met inclusion criteria. None of the 67 patients included had known adrenal insufficiency prior to TSS. A POD 1 and POD 5 morning total serum cortisol was obtained in all 67 patients. Hydrocortisone was started on all patients after a POD1 serum cortisol was obtained. If POD 1 and POD 5 morning cortisol were both ≥ 18 μg/dL, hydrocortisone was discontinued. If either POD 1 or POD 5 were < 18 μg/dL, hydrocortisone was continued and 3-4 weeks postoperatively a 1μg cortrosyn stimulation test (CST) was performed. The ability of POD 1 or POD 5 cortisol to predict HPA function was determined using standard confusion matrix calculations and receiver-operator control curve analysis.

RESULTS: Forty-three patients required a 1 μg CST for definitive assessment of the HPA axis. A POD 1 serum morning cortisol ≥ 18 μg/dL had poor sensitivity (51%) and specificity (33%) for predicting an intact HPA axis. A POD 5 serum cortisol ≥ 18 μg/dL predicted an intact HPA axis with poor sensitivity (25%), but 100% specificity. A POD 5 serum cortisol ≥ 15 μg/dL increased the sensitivity to 51% and maintained specificity at 100%.

CONCLUSION: A POD 5 morning cortisol level ≥ 15 μg/dL is a specific predictor of normal HPA function in post-operative pituitary adenoma patients. The specificity of this test is vitally important as a missed diagnosis of adrenal insufficiency may result in morbidity or mortality.

Disclosure: The authors have no relationships to disclose.

P33

Long-Term Weight Development and Psychosocial Status in Childhood Craniopharyngioma Patients

Anthe S. Sterkenburg[1,2], Anika Hoffmann[1], Ursel Gebhardt[1], Hermann L. Müller[1*]

*Department of Pediatrics, Klinikum Oldenburg, Oldenburg, Germany; Childrens´ Hospital, UMCG, University of Groningen, The Netherlands. *for the study committee of KRANIOPHARYNGEOM 2000 / 2007.*

Background: Craniopharyngioma (CP) are the most common sellar tumors in children. Patients often develop excessive weight gain and obesity due to several factors as involvement or damage of the hypothalamus. Previous studies on the weight development in craniopharyngioma patients have shown an increase in weight before and in the first ten years after diagnosis leading to an impaired quality of life. The long-term weight development in these patients has not been investigated till now.

Methods: In a retrospective study, we analysed the weight development of 108 craniopharyngioma patients who were diagnosed before 2001. Data from physical examinations, anthropometric measurements and the patient's records were used, as well as a questionnaire answered by the patients in 2011 on their current weight and psychosocial status. The BMI of CP patients at diagnosis, 8-12 years after diagnosis, during long-term follow-up and at the time they answered the questionnaire was analysed and factors were investigated for their effect on the weight development.

Results: Long-term survivors of CP were assessed at a median age of 26.1 years (range 14.8-42.7) after a median follow-up of 17.01 years (range 8.81-33.40) after CP diagnosis. All patients show an increase in BMI during the first ten years after diagnosis, as previously published. However, during long-term follow-up (more than 12 years after diagnosis) no further weight increase is seen. Patients with hypothalamic involvement of CP develop a higher initial weight increase, but also a stabilisation of BMI as well. Patients with a normal BMI at diagnosis (-2 to +2SD) show the highest weight increase during the first ten years after diagnosis, whereas patients presenting with obesity at diagnosis (BMI>3SD) show a smaller increase in BMISDS during long-term follow-up. Conclusion: We conclude that the degree of obesity in CP reaches a certain plateau during long-term follow-up.

Disclosure: The authors have no relationships to disclose.

P34

Outcome of Microscopic Versus Endoscopic Surgery for Nonfunctional Pituitary Adenomas at The Helsinki University Central Hospital

Atte Karppinen[1], Satu Vehkavaara[2], Leena Kivipelto[1], Emmi Tikkanen[3], Riku Kivisaari[1], Elina Ritvonen[2], Mika Niemelä[1], Camilla Schalin-Jäntti[2]

[1]Department of Neurosurgery, Helsinki University Central Hospital; [2]Division of Endocrinology, Department of Medicine, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; [3]Institute for Molecular Medicine Finland, National Institute for Health and Welfare, Finland

Objectives: 331 consecutive patients were operated on at Helsinki University Central Hospital (HUCH) between 2000 and 2010 because of a newly diagnosed pituitary adenoma. The transsphenoidal microscopic technique (Mscope) was replaced by the endoscopic technique (Escope) in June 2008. The aim was to retrospectively compare outcome of Mscope (n= 103) to Escope (n= 33) in patients with nonfunctional pituitary adenomas (NFPA).

Methods: Complication rates, operation time, tumor size, KNOSP-grade, visual acuity/fields, prevalence of anterior hypopituitarism (Hypopit) and diabetes insipidus (DI) were compared between the groups before, 3 and 12 months after surgery. Tumor control was evaluated by MRI, visual acuity/fields by a neuro-ophthalmologist and pituitary function by standard assays and need for replacement therapy.

Results: Preoperatively there was no statistical difference between the groups in mean tumor diameter (27.9 mm in Mscope vs. 27.3 mm in Escope), invasive KNOSP-grades (81.6% vs 87.9%), Hypopit (53.9% vs 54.5%) nor visual field defects (59.8% vs 75.8%) (P=0.25). Postoperative cerebrospinal fluid leak occurred in 2.9% vs 9.1% (P=0.15), hemorrhage in 2.1 vs 6.1%, (P=0.35), and meningitis in 1.9% vs 9.1% (P= 0.09). Operative time was 92 min in Mscope and 102 min in Escope (P= 0.12). After 3 months, mean residual tumor diameter was 15.6 mm vs 11.4 mm (P=0.10) and total tumor removal was achieved in 42.7% vs 57.6% (P=0.09). Visual fields had normalized or improved in 86.2% vs 84%, (P=0.52). Hypopit was present in 65.3% vs 63.6% (P=0.51) and DI 6.9% vs 0% (P=0.14). At 12 months, Hypopit was present in 61.2% vs 65.5% (P=0.79) and DI 2.4% vs 0% (P=0.55).

Conclusions: Better tumor control but more complications (CSF leak, meningitis) and longer operative time were related to the introduction of endoscopic technique. Visual and hormonal outcomes were similar, however DI was related to Mscope only.

Disclosure: The authors have no relationships to disclose.

P35

Pituitary Dysfunction After Aneurysmal Subarachnoid Hemorrhage. Is There a Difference Between Middle Cerebral Artery and Anterior Communicating Artery Aneurysms?

Kanchan Kumar Mukherjee[1], Pinaki Dutta[2], Prashant Kumar Chaudhary[1], Shariq Rashid Masoodi[3], Srinivasan Anand[4], Ashis Pathak[5], Viral N Shah[6], Suresh Narain Mathuriya[1]

[1]Neurosurgery, Post Graduate Institute of Medical Education and Research, Chandigarh, India, [2]Endocrinology, Post Graduate Institute of Medical Education and Research, Chandigarh, India, [3]Endocrinology, SKIMS, Srinagar J&K, India, [4]Pharmacology, Post Graduate Institute of Medical Education and Research, Chandigarh, India, [5]Neurosurgery, Ward 4, Hull Royal Infirmary, United Kingdom, [6]Post Graduate Institute of Medical Education and Research, Chandigarh, India

Background: The data on incidence of hypopituitarism after Subarachnoid hemorrhage (SAH) are conflicting. Furthermore, it is still not known whether there is any difference in hormonal deficiencies between SAH due to anterior communicating artery (A-Com) and middle cerebral artery (MCA) aneurysms.

Material and Methods: This study includes both retrospective and prospective arms. The data collected included baseline demographic profile, clinical severity on admission to the hospital by the Hunt and Hess grading system and World Federation of Neurological Surgeons (WFNS) grading, radiological severity of bleed by the Fisher's classification, and treatment details. All the patients underwent detailed hormonal evaluation at baseline and 6 months in prospective group while at the end of 1 year in the retrospective group. Hormonal deficiencies between patients with A-Com and MCA aneurysmal SAH were compared using appropriate statistical tests.

Results: Of 80 patients studied, 47 patients (A-Com: 28 and MCA: 19) were in the retrospective group, while 33 patients (A-Com 19, MCA 14) were in the prospective group. The baseline data were comparable between the two groups. At or after 6 months follow-up, 25(31.2%) patients, 13 patients with A-Com and 12 patients with MCA aneurysmal SAH, had some form of hormone deficiency. Furthermore, there was no difference in endocrine dysfunctions between the two groups. There was no correlation between the severity of hormonal deficiency and the clinical severity of SAH grade by Hunt and Hess and radiological grade of SAH by Fisher's grade.

Conclusion: Hormonal deficiencies are not uncommon in patients with SAH. There is no difference in hormonal deficiencies and severity of hypopituitarism in patient with SAH due to A-Com and MCA bleed.

Disclosure: The authors have no relationships to disclose.

P36

Predictive Role of Inflammatory Cytokines and Neurotrophic Factors Plasma Levels on Pituitary Function After Ischemic and Hemorrhagic Stroke

[1]Marta Bondanelli, [1]Maria Rosaria Ambrosio, [2]Susanna Lavezzi, [1]Alessandra Malaspina, [2]Antonella Bergonzoni, [2]Nino Basaglia, [1]Ettore degli Uberti, [1]Maria Chiara Zatelli

[1]Section of Endocrinology, Dept. of Medicine, University of Ferrara, Italy; [2]Dept. of Rehabilitation Medicine, St. Anna Hospital of Ferrara, Italy

Stroke may be associated with hyopituitarism, possibly influencing neurological recovery. Increasing evidence suggests a role for pro-inflammatory cytokines in the ischemia-induced neuronal damage, which may be attenuated by neurotrophic factors. We investigated the possible role of inflammatory cytokines and neurotrophic factors on hypopituitarism associated with stroke. The predictive value of these factors on outcome was also evaluated. We measured plasma levels of interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), glial derived neurotrophic factor (GDNF), nerve growth factor (NGF), and vascular endothelial growth factor (VEGF) in 29 patients [8 F; mean (±SEM) age 55.4±2.2 yr; 17 ischemic (IS), 12 hemorrhagic (HE)] with hypopituitarism (17 GH, 9 LH/FSH, 1 TSH, 2 GH + LH/FSH deficit) and in 43 patients (22 F; mean age 51.2±2.2 yr; 23 IS, 20 HE) with normal pituitary function, evaluated from 1 to 6 months after stroke during the in-patient rehabilitation period. At time of evaluation HE patients had greater neurological impairment compared with IS patients, and showed higher ($p<0.05$) GDNF (245±47 vs. 76±18.9 pg/ml) and IL-6 (14.1±3 vs. 7.7±1.7 pg/ml) and lower ($p<0.05$) TNF-α (1.2±0.2 vs. 2.82±0.6 pg/ml) and fibrinogen (294±19 vs. 351±13 mg/dl) levels. GDNF was particularly higher in HE hypopituitary patients compared with normal HE (296±88 vs. 217±56 pg/ml, $p<0.05$), whereas TNF-α (3.8±1.3 vs. 0.77±0.06 pg/ml, $p<0.01$) was higher in all hyopituitary patients compared with normal patients. IL-6 positively correlated with ACTH and cortisol levels, and negatively with estradiol or testosterone levels, and with outcome indexes the end of the inpatients rehabilitation. Neurological improvement during rehabilitation was better in patients with normal pituitary function. In conclusion, high inflammatory cytokine levels in post-acute phase of IS and HE stroke may be associated with hypopituitarism and/or poor outcome. Elevated GDNF levels in HE patients, with greater neurological impairment, may indicate a greater attempt to promote neurogenesis.

Disclosure: The authors have no relationships to disclose.

P37

Recovery from Hypogonadotrophıc Hypogonadısm in a Young Woman wıth Perıpartum Hypophysıtıs After Steroıd Replacement Therapy

Nurdan Gül, Mustafa Altınkaynak, Sema Yarman

Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, Istanbul, Turkey

A 31-year-old woman presented with hypopituitarism and a decreased pituitary size on magnetic resonance imaging (MRI). About a year ago, during the last trimester of her first pregnancy, she experienced severe headaches and hypotension. Her physical examination and cranial MRI were reported to be unremarkable. Her severe headaches had resolved ten days before delivery. She gave birth at term with epidural anesthesia to a healthy boy without complications. She couldn't breastfeed the baby, and she was amenorrheic for over a year after delivery. She also reported to experience mild headaches infrequently. She was referred to our clinic since her hormone profile was compatible with hypopituitarism. Reevaluation of the previous cranial MRI revealed an enlarged pituitary gland that could be explained by pregnancy. Her thyroid autoantibodies were positive. She started to receive replacement therapy with prednisolon and thyroxine and later gonadal hormones with a presumptive diagnosis of autoimmune lymphocytic hypophysitis. She regained normal gonadal function a few months after steroid replacement therapy. However, she has still been on prednisolon and thyroxine replacement during the follow-up period for more than one year. The natural history of lymphocytic hypophysitis indicates that it can evolve in different ways, our report suggests that resolution of hypogonadism may occur with steroid replacement.

Disclosure: The authors have no relationships to disclose.

P38

Three Cases with Hypogonadism, Polyuria and Polydipsia as Presenting Manifestations of Neurosarcoidosis

Nurdan Gül, Refik Tanakol, Sema Yarman

Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, Istanbul, Turkey

Objectives: Sarcoidosis is a systemic granulomatous disorder. Central nervous system involvement occurs in approximately 5% of patients, and systemic manifestations usually preceed neurological findings. We retrospectively reviewed our patients with sarcoidosis and identified 3 patients with neurosarcoidosis who all presented with hypogonadism, polyuria and polydipsia.

Design: This was a single centre, retrospective analysis of 3 patients with a minimum follow-up of 1 year.

Methods: Case analysis included clinical, biochemical, histological, endocrinological evaluation and imaging of involved organs as primary evaluation and in response to corticosteroid therapy.

Results: Diagnosis of neurosarcoidosis was confirmed in all patients with proven additional extracerebral manifestations. One of the patients was diagnosed as pulmonary sarcoidosis before neurologic symptoms and pituitary dysfunction started. Neurologic symptoms and pituitary dysfunction were the presenting findings in the other two patients. Two patients were diagnosed as central diabetes insipidus. Water deprivation test of the third patients was normal. This finding was explained as possible alteration of drink behavior mediated by central effects exerted on the hypotalamic centers regulating thirst and fluid balance. The symptoms began just after delivery in one patient, and postpartum lymphocytic hypophysitis was among the differential diagnosis. Cranial MRI, pulmonary findings and granulomatous lesions on lip biopsy were suggestive of systemic involvement of sarcoidosis. All of the patients received corticosteroids. Pituitary dysfunction remained unchanged or deteriorated despite corticosteroid therapy. Two of the patients died of sarcoidosis during follow-up and the third patient lost follow-up after five years.

Conclusions: The presenting symptoms of neurosarcoidosis may vary. The occurence of hypogonadism with polyuria and polidipsia is suggestive of neurosarcoidosis. Especially for females in the postpartum period the diagnosis of neurosarcoidosis may be challenging. Also, polyuria and polydipsia may not always be indicative of central diabetes insipidus in the context of neurosarcoidosis.

Disclosure: The authors have no relationships to disclose.

P39

Two Successive Pregnancies with Diabetes Insipidus

Güzide Gonca Oruk, Mitat Bahceci, Ahmet Gorgel, Devrim Dolek Cetinkaya, Fusun Salgur, Mustafa Demirpence

Izmir Katip Celebi University Ataturk Training and Research Hospital, Division of Endocrinology and Metabolism, Izmir, Turkey

Diabetes insipidus can complicate up to 1 in 30,000 pregnancies. Diabetes insipidus during pregnancy has multiple causes. Polyuria and polydipsia can occur or be exacerbated in women with overt or subclinical central or nephrogenic diabetes insipidus. In some forms of diabetes insipidus pregnancy may be complicated, including preeclampsia. Management of central diabetes insipidus and transient diabetes insipidus of pregnancy can be achieved with 1-deamino-8-D-arginine vasopressin (desmopressin acetate) (DDAVP). Because of its rare occurence, we report a case of a woman with a preexisting diabetes insipidus (DI) due to pituitary surgery, who had two consecutive uncomplicated pregnancies. Both pregnancies resulted after spontaneous conception in the same year and had a similar uneventful course. At the time of conception the patient was receiving levothyroxin replacement treatment and DDAVP 20 μg/day which maintained a urinary volume of 4-4.5 l/day. During gestation the dose was increased to 40μg/day. She was followed closely with urine output, urine dansity, electrolytes, liver function tests and the fetus was also monitored for oligohydramnios by the obstetrics clinic. No complication was experienced during labor. The children are 36 and 25 months old and healthy without any anomaly. Pre-existing DI can be handled carefully and result in an uncomplicated pregnancy. Increased awareness of diabetes insipidus in pregnancy may lead to appropriate treatment that will reduce the risks of maternal and fetal morbidity. Also growing experience with DDAVP treatment has shown that it is a safe and effective treatment for diabetes insipidus in pregnancy.

Disclosure: The authors have no relationships to disclose.

Prolactin

P40
High Frequency of Headache in Patients with Hyperprolactinemia

Andreia P. Klein, Luiza Fitarelly, Carolina G. S. Leães, Julia F. S. Pereira-Lima, Liselotte M. Barea, Miriam da Costa Oliveira

Center of Neuroendocrinology / Santa Casa of Porto Alegre – UFCSPA, Porto Alegre, Brazil

Introduction: Headache is a common manifestation of pituitary adenomas, particularly prolactinomas. The neuroendocrinology participation in the genesis of headache in these tumors has been strongly suggested, and hyperprolactinemia can contribute to the development of pain, probably by neuro-sensory modulation.

Objective: To evaluate the frequency and characteristics of headache in patients with hyperprolactinemia.

Patients and methods: We evaluated, through a questionnaire on headache, 71 patients with a previous diagnosis of hyperprolactinemia, 53 females (74.6%), mean age of 43 years (range 16-85), mean duration of diagnosis of 8.6 years (0-37 years) and follow-up time of 5.2 years (0-23). Regarding the etiology of hyperprolactinemia, 45.3% of patients had macroprolactinomas, 26.7% microprolactinomas and 27.9% hyperprolactinemia due to other causes (idiopathic or drug-induced). Data from etiology, serum prolactin value in the presentation and in those with adenomas, tumor volume, and presence of invasion, documented by magnetic resonance imaging of the pituitary were collected.

Results: The overall prevalence of headache in patients with hyperprolactinemia was 64.7% and the phenotype of migraine was ranked in most patients (70.9%), followed by tension headache (14.5%). Among the causes of hyperprolactinemia, invasive macroprolactinomas were most associated with headache (80%), followed by microprolactinomas (71.4%) and non-invasive macroprolactinomas (66.7%). Dopamine agonist therapy alone was instituted in 47 patients (59.1%), and surgery and radiotherapy performed in 17 and 5 patients, respectively. In assessing patients on normoprolactinemia, 94.7% reported improvement in headache (mean prolactin levels of 28.9 ng / ml). Among patients who remained with hyperprolactinemia (mean of 110.7 ng / ml) despite treatment, 52.9% reported improvement in headache.

Conclusions: Headache was a common finding in patients with hyperprolactinemia (64.7%), especially in invasive macroprolactinomas and the predominant phenotype was migraine. The treatment of hyperprolactinemia is associated with improvement of symptoms.

Disclosure: The authors have no relationships to disclose.

P41
Masked Hyperprolactinemia: Tumor-Derived Factors Inhibiting Prolactin Secretion Caused by Pituitary-Stalk Damage

Yasuyuki Kinoshita[1], Atsushi Tominaga[1], Satoshi Usui[1], Kazuhiko Sugiyama[2] and Kaoru Kurisu[1]

[1]Department of Neurosurgery, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan; [2]Department of Clinical Oncology and Neuro-oncology Program, Hiroshima University Hospital, Hiroshima, Japan

Object: Tumor-induced secondary hyperprolactinemia in patients with non-prolactin (PRL)-secreting pituitary tumors has conservatively been ascribed to pituitary-stalk damage; however, this hypothesis remains unresolved to date. The authors examined the influence of pituitary-stalk damage on secondary hyperprolactinemia physically and endocrinologically. Furthermore, the effect of tumors-derived factor from the tumors; leukemia inhibitory factor (LIF) of pituitary adenomas was evaluated.

Methods: The authors conducted a retrospective analysis of secondary hyperprolactinemia in 106 (female: 55; male: 51) operated patients (mean age: 57.5 years) diagnosed with pituitary adenomas postoperatively. Pituitary adenomas showing PRL-positive immunostaining were omitted from the study. The incidence of secondary hyperprolactinemia was evaluated, and pituitary-stalk damage was derived physically by assessing the radio-graphical configuration on magnetic resonance imaging (MRI) and endocrinologically by monitoring hormonal functions of the anterior pituitary lobe using the insulin-induced hypoglycemia test. Moreover, the effect of a tumor-derived intrasellar factor; LIF on secondary hyperprolactinemia was examined. The institutional ethics committee approved the experimental protocol used (no. 162, 2009).

Results: Although preoperative hyperprolactinemia was observed in 31 (29.2%) patients, 28 (90%) of them were normalized during a postoperative 3-month period. Parameter monitoring indicated that the observed hyperprolactinemia was not correlated with either the physical stalk compression by tumors (MRI findings) or the incidence of endocrinological dysfunction (provocation test). However, the tumor-derived intrasellar factor (LIF) showed a negative correlation with prevailing hyperprolactinemia ($p < 0.01$).

Conclusions: Although secondary hyperprolactinemia might be caused by pituitary-stalk damage, any statistical significance could not be found between secondary hyperprolactinemia and pituitary-stalk damage. Tumor-derived factor (LIF) might display masking effects on the onset of secondary hyperprolactinemia.

Disclosure: The authors have no relationships to disclose.

P42
Microprolactinomas Evolution After Menopause

Susana Mallea-Gil, Marcos Manavela, Analía Elena Alfieri, Maria Carolina Ballarino, Alberto Benjamin Chervin, Karina Danilowicz, Sabrina Diez, Patricia Fainstein Day, Natalia Garcia Basavilbaso, Mariela Glerean, Mirtha A. Guitelman, Débora Adela Katz, Marcela Martinez, Karina Miragaya, Daniel Moncet, Amelia Rogozinski, Marisa Gladys Servidio, Graciela Stalldecker, Marcelo N. Vitale, Maria de Lujan Calcagno, Laura Boero

Neuroendocrinology Department (Departamento de Neuroendocrinología), Sociedad Argentina de Endocrinología y Metabolismo. Buenos Aires, Argentina

Introduction: The stimulatory role of estrogen on prolactin secretion and on proliferation of lactotropic cells is well-established. There is scarce literature about the effects of menopause in patients with prolactinomas.

Objectives: To assess the evolution of the tumor size and prolactin (PRL) levels in patients with microprolactinomas diagnosed and treated with dopamine agonists (bromocriptine (BEC)/cabergoline (CAB) during their fertile age and the effects of the suspension of those drugs after menopause.

Material and methods: retrospective, multicenter study. Twenty-two patients with microprolactinomas diagnosed during their fertile age were studied in their menopause. Mean±SD age at menopause was 49±3.6 years. In all patients treatment was stopped when they reached menopause.

Results: Mean±SD pre-treatment PRL level was 117±60 ng/ml and after stopping treatment was 17±6.8 ng/ml. During menopause and before stopping treatment, the tumor disappeared in 9 and the tumor size decreased in 13 patients; a year after treatment suspension, the tumor disappeared in 2/13 and it was unchanged in 11/13.The mean ± SD treatment duration had been 113±75 months. The period between the suspension of treatment and the last assessment was: 0-15 years. Two patients were restarted on treatment because PRL levels increased.

Conclusions: Normal PRL levels and sustained reduction or disappearance of adenomas were achieved in most of the patients studied. Only two out of 22 restarted treatment because of hyperprolactinemia. Dopamine agonists might be safely stopped after menopause in patients with microprolactinomas.

Disclosure: The authors have no relationships to disclose.

P43
Second Attempt to Withdraw Cabergoline in Hyperprolactinemia

Ratchaneewan Kwancharoen, Renata Simona Auriemma, Gayane Yenokyan, Gary S. Wand, Annamaria Colao, Roberto Salvatori

Division of Endocrinology and Metabolism, Department of Medicine (R.K., G.S.W., R.S.), Johns Hopkins University School of Medicine, Johns Hopkins University School of Public Health (G.Y.), Baltimore, Maryland, USA, Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, University "Federico II", Naples, Italy (R.S.A., A.C.)

Introduction: According to Pituitary Society recommendation, cabergoline (CAB) therapy can be discontinued after 2 years in hyperprolactinemia patients who fit certain criteria. Previous studies found recurrence rates of 40-60%. Whether CAB therapy can be successfully discontinued after one unsuccessful withdrawal is unknown.

Methods: We conducted a prospective two-center study on a second attempt of CAB withdrawal. Inclusion criteria were: 1) recurrence of hyperprolactinemia after first withdrawal; 2) additional CAB therapy for at least 2 years; 3) normal serum prolactin before second withdrawal; 4) CAB dose ≤1 mg/week. Prolactin level was monitored after discontinuing therapy. Predictors of time to second recurrence were studied. The median follow up time was 6.05 months (1-60). Median follow up time for patients who are still in remission was 36 months (7-60).

Results: A total of 17 patients were recruited. Mean age was 41± 17.3 yrs. 65% were female. Initial tumors size were microadenoma in 59 %, macroadenoma in 41%. The average CAB dose at withdrawal was 0.38±0.2 mg/wk (median= 0.25, range 0.175-1). Ten of 17 patients (59%) recurred. Median time to recurrence was 6 months. The incidence of overall recurrence rate was 41 events per 100 person-years. The estimated cumulative hazard of recurrence was 40% and 84% at 6 and 12 months respectively. The probability to be recurrence-free at 6 and 12 months was 65% and 40%, respectively. Age, gender, initial tumor size, prolactin level, CAB dosage at time of withdrawal, and treatment duration were not found to be predictors of recurrence.

Conclusion: Second attempt of CAB withdrawal after 2 additional years of therapy may be successful in some patients. A second withdrawal can be attempted with close monitoring of prolactin level. In this study, we could not identify any predictor of recurrence. Most of the recurrences occurred within the first 6 months after withdrawal.

Disclosure: The authors have no relationships to disclose.

Tumors

P44
'Atypical' Pituitary Adenomas – Clinical Value of the WHO Pathological Criteria

Monique L Costin[1], Tint Tint Shein[2], Peter Earls[2], Ann McCormack[1]

[1] Department of Endocrinology, St Vincent's Hospital, Sydney, Australia [2]Department of Anatomical Pathology, St Vincent's Hospital, Sydney, Australia

Background: Identification of aggressive pituitary tumours is important in that it may influence the approach to patient management. The 2004 WHO pathological criteria defined the 'atypical' pituitary adenoma (a tumour with increased mitotic rate, Ki67 and p53 expression) in an attempt to identify a group of tumours that may behave more aggressively.

Objectives: To determine the prevalence of 'atypical' pituitary tumours amongst a 10 year cohort of pituitary tumours. To evaluate how well the WHO criteria predict clinically aggressive pituitary tumours.

Methods: Pathological data was collected on all patients who underwent pituitary surgery between January 2000 and December 2009. Tumours with Ki67 >3%, nuclear p53 staining >40% and mitotic rate >2 per 10 high-power fields were classified as meeting atypical criteria according to the WHO.

Data was collected from patient records, including tumour subtype, size, Hardy's grade and clinical outcome. Aggressive tumours were defined as those with progressive growth despite >3 standard therapies (medical, surgery, radiotherapy).

Results: 9/66 tumours (13.6%) had 'atypical' features. Two had Ki67 >3%, 7 had extensive nuclear p53 staining and none had an increased mitotic rate. No case demonstrated more than one atypical criterion.

Average clinical follow-up was 74.3 months. Six patients with aggressive pituitary tumours were identified: none had Ki67 >3% or an increased mitotic rate, one tumour had extensive nuclear p53 staining and another had other abnormal morphological features. Twelve patients had tumour recurrence during follow-up, none of which met any of the WHO atypical criteria.

Conclusions: 15% of a 10-year cohort of pituitary tumours displayed atypical features as defined by the 2004 WHO criteria. However, none became aggressive in the follow-up period. Furthermore, the WHO criteria failed to identify those tumours that did become aggressive. We recommend additional validation of the WHO criteria be performed in larger cohorts.

Disclosure: The authors have no relationships to disclose. This abstract 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.

P45
A New Prognostic Clinicopathological Classification of Pituitary Endocrine Tumors: A Multicentric Case-Control Study of 410 Patients with 8 Years Post-Operative Follow-Up

Jacqueline Trouillas[1], Pascal Roy[2], Emmanuelle Dantony[2], Carole Auger[1], Emmanuel Jouanneau[1], Gérald Raverot[1] and the members of HYPOPRONOS

[1]INSERM, UMR-S1028, Lyon Neuroscience Research Center, Oncoflam Team, Lyon, F-69372, France, Université Lyon 1, Hospices Civils de Lyon, Lyon, France; [2]CNRS; UMR 5558, Equipe Biostatistique Santé, Pierre-Bénite, France, Service de Biostatistique, Hospices Civils de Lyon, Lyon, France

Pituitary endocrine tumors are currently classified by histological, immunocytochemical and numerous ultrastructural characteristics lacking unequivocal prognostic correlations. We investigated the prognostic value of a new clinicopathological classification with grades based on invasion and proliferation, the components of tumor behavior. This retrospective multicentric case-control study comprised 410 patients who had surgery for a pituitary tumor with long-term follow-up. Using pituitary magnetic resonance imaging for diagnosis of cavernous or sphenoid sinus invasion, immunocytochemistry, markers of the cell cycle (Ki-67, mitosis) and p53, tumors were classified according to size (micro, macro and giant), type (PRL, GH, FSH/LH, ACTH and TSH) and grade (grade1a: non-invasive; 1b: non-invasive and proliferative; 2a: invasive; 2b: invasive and proliferative; and 3: metastatic). The association between patient status at 8-years follow-up and age, sex, and classification was evaluated by 2 multivariate analyses assessing disease- or recurrence/progression-free status. At 8 years after surgery, 195 patients were disease-free (controls) and 215 patients were not (cases). In 125 of the cases the tumors had recurred or progressed. Analyses of disease-free and recurrence/progression-free status revealed the significant prognostic value ($p<0.001$; $p<0.05$) of age, tumor type, and grade across all tumor types and for each tumor type. Invasive and proliferative tumors (grade 2b) had a poor prognosis, with an increased probability of tumor persistence or progression of 25- or 12-fold, respectively, compared to non-invasive tumors (grade 1a). This new, easy to use clinicopathological classification of pituitary endocrine tumors has demonstrated its prognostic worth by strongly predicting the probability of post-operative complete remission or tumor progression and so could help clinicians choose the best post-operative therapy.

Disclosure: The authors have no relationships to disclose.

P46

Atypical Pituitary Adenomas: A Monocentric Retrospective Observational Study

Chiloiro S.[1], Bianchi A.[1], Giampietro A.[1], Lugli F.[1], Mormando M.[1], Iacovazzo D.[1], Piacentini S.[1], Tartaglione L.[1], Doglietto F.[2], Anile C. [2], Maira G. [2], Pontecorvi A.[1], De Marinis L.[1]

[1]Endocrinology, [2]Neurosurgery, Catholic University, Policlinico "A. Gemelli", Rome – Italy

Introduction: In 2004, the WHO defined atypical pituitary adenomas (APAs) those with Ki-67>3%, excessive p53 expression and increased mitotic activity. The usefulness of this new classification is still controversial.

Aims: To investigate the clinical, neuroimaging and immunohistochemical (IHC) features in a series of atypical pituitary adenomas.

Materials and methods: We retrospectively reviewed 299 consecutive PAs, operated on in the department of Neurosurgery at our Institution and followed up in the last 8 years at the Hypothalamic-Pituitary Disease Unit of the same institution. APAs represented 12.7% of cases. 73.7% of APAs patients were female and 26.3% were male. Age at diagnosis was higher in APAs, compared to TPAs (p=0,008). Among APAs, 79% were functioning tumors (31.6% GH-secreting, 23.7% prolactinomas, 21.1% ACTH secreting, 2.6% TSH-omas) and 21% were NFPAs. ACTH-secreting PAs had a higher chance to be APAs (p=0,014) HR 2,69 (1,22-5,92). These data are confirmed by IHC evaluation: in atypical NFPAs, we found 50% null-cell, 25% TSH-staining and 25% ACTH-staining positive PAs; in atypical-functioning PAs, we found 26,7% GH-staining and 26,7% PRL-staining positive PAs. Among APAs, 78.9% were macroadenomas; 39.5% were confined to the sella, 15,8% were Wilson-A, 21,1% were Wilson-E and 23,7% extended to the cavernous sinus and other sites. Radical surgery was obtained in 68,4% of APAs; recurrence occurred in 46,2% of APAs. Tumor size, extension and neurosurgical outcome didn't differ between APAs and TPAs. 71,1% of APAs needed adjuvant treatments after neurosurgery (medical, radiotherapy or neurosurgery). Only 28,9% of APAs were cured after the first neurosurgical treatment.

Conclusion: Although APAs and TPAs didn't significantly differ for clinical, neuroimaging and IHC features, we suggest to plan a more adequate short-term follow up and, if necessary, a more aggressive therapeutic schedule in APAs.

Disclosure: The authors have no relationships to disclose.

P47

Cabergoline Effectiveness in Patients with Clinically Nonfunctioning Pituitary Adenomas

Rafael Loch Batista, Nina Rosa de Castro Musolino, Valter Cescato, Gilberto Ochamn da Silva, Malebranche Berardo Carneiro da Cunha Neto

Neuroendocrine Unit, Divison of Functional Neurosurgery, Hospital das Clinicas, University of S.paulo Medical School, Sao Paulo, Brazil

Surgery is the treatment of choice for the most patients with Clinically Nonfunctioning Pituitary Adenomas (NFPA). Although surgery is efficient in relieving symptoms related to tumor compression, complete surgical resection is not frequent and radiotherapy is required in many cases. The role of dopamine agonists has not yet been well established in NFPA.

Objective: To evaluate the useful of cabergoline in NFPA patients with residual tumor after transsphenoidal (TS) surgery, in reducing and/or maintain a stable tumor rest.

Methods: We compared two groups of NFPA patients who presented residual tumor in a MRI performed six months after surgery: 37 patients treated by cabergoline, dose from 1.5 to 3.5mg/week (A) and 31 patients followed without cabergoline (B). No patients were treated by irradiation before or during the follow-up. All patients were evaluated every 6 months with MRI for 12 months. Twenty-eight patients received de maximum dose of cabergoline (3.5mg/w) in the Group A. Change of tumor volume bigger than 15% were considering significant. Statistical analysis was performed using the statistical program SOFA.

Results: The MRI in group A showed stabilization of residual tumor in 67.6% (25/37) and tumor reduction in 29.7% (11/37) of patients, while tumor progression was observed in only one patient (2.7%). In group B, stabilization was observed at 80.6% (25/31), reduction in 3.2% (1/31) and growth in 16.1% (5/31) of patients. Statistical difference between groups A and B was obtained regarding tumor reduction (29.7% vs. 3.2%, p = 0.02) and tumor progression (2.7% vs. 16.1%, p <0.01) with no difference in the stabilization of residual tumor (p = 0.06).

Conclusions: Cabergoline, after TS surgery, was useful in reducing or stabling residual tumor in significant number of NFPA patients in a 12-month follow up.

Disclosure: Nina Musolino is a speaker for Pfizer; Rafael Loch Batista, Valter Cescato, Gilberto Ochamn da Silva, and Malebranche Berardo Carneiro da Cunha Neto have no relationships to disclose.

P48
Coexistence of a Pituicytoma and a Non-Functioning Pituitary Adenoma

Carvalho D[1], Carvalho B[2], Oliveira AI[1], Polónia P[2], Rios E[3], Basto M[4], Castro L[3], Pereira J[2], Vinha E[1], Vaz R[2]

[1]Endocrinology, Diabetes and Metabolism, [2]Neurosurgery, [3]Pathology, [4]Neuroradiology, Centro Hospitalar S. João/ Faculty of Medicine University of Porto Portugal, Porto, Portugal

Introduction: Pituicytoma is an extremely rare tumour and accounts for 0.45% of all non-adenomatous lesions and 0.07% of sellar lesions. Only 60 cases were reported in the literature. It originates in the neurohypophysis and arises from local supporting glial cells named pituicytes. Typical clinical features are bitemporal hemianopia and hypopituitarism secondary to mass effect. Diagnosis relies on histological and immunohistochemical criteria.

Case report: 60-year-old male presenting with progressive deterioration of visual acuity (3/10 on the right eye and bitemporal hemianopia with left temporal field predominant loss). MRI disclosed sellar lesion (Hardy II D) compatible with a diagnosis of pituitary macroadenoma. There were no signs or symptoms of hyper or hyposecretion of pituitary hormones. Endoscopic transsphenoidal partial removal has been hampered by hemorrhagic characteristics of the tumour. Postoperatively there was significant improvement in visual acuity without diabetes insipidus. Histological examination revealed a WHO grade II fibrillary astrocytoma - moderate cellular density, and densely fibrillary material, low mitotic index, immunohistochemistry positive for vimentin and GFAP (glial fibrillary acidic protein). Postoperatively, MRI evaluation reveals a persistence of a pituitary lesion. The patient was submitted to subfrontal reoperation and the diagnosis was non-functioning pituitary adenoma with focal FSH positivity. The patient maintains normal pituitary function, although he recently presents erectile dysfunction.

Conclusions: Pituicytomas are rare tumours, but the coincident of 2 histologically different tumours is extremely rare. Gross surgical resection is the treatment of choice. The pathophysiological implications of the 2 coexisting conditions raise important questions: two lesions with different origins? Which is the first and what is the influence of one on the other?

Disclosure: The authors have no relationships to disclose.

P49
Cystic Tumors of Sellar Region: Usefulness of Hormone Intra-Cyst Evaluation

Borba CG[1], Musolino NR[2], Cescato VAS[2], Silva GO[2], Cunha Neto MBC[2]

[1]Hospital Santa Marcelina - Departamento de Endocrinologia, [2]Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - Divisão de Neurocirurgia Funcional. Sao Paulo, SP, Brasil

The diagnosis of sellar masses includes possibilities as diverse as craniopharyngioma, Rathke's cyst, adenoma, abscess, metastasis and others. The correct diagnosis can be difficult in some cases, especially if there is no material for immunohistochemistry (ICQ). We describe the hormone dosage in the liquid obtained by cyst puncture in a case index and in other 15 cases. Objective: To evaluate the contribution of hormonal dosage in the cystic material for the differential diagnosis. Case index: female prolactinoma patient treated by bromocriptine for 23 years. During follow-up, a 4cm cystic lesion in the parietal region was diagnosed. Prolactin dosage in the cystic liquid obtained by stereotactic puncture was 160.000ng/mL confirming metastasis of prolactinoma. Dosage of pituitary hormones in material of cyst puncture sealing during surgery in 15 patients (11 women), age 42y (28-66) with solid-cystic lesions (n = 14) or purely cystic (n = 1), median diameter of 30mm (12-40). The results were analyzed together with serum and histophatological examination. The serum PRL was high in 9 cases: 193ng/mL (38-2115). In 3 of them under 150ng/mL. The dosage of PRL in the cyst ranged from 6 to 102827ng/mL. Values >3000ng/mL observed in 9 cases, all of them with PRL in ICQ, buth serum PRL was normal in one and only slightly elevated in another (54ng/mL). The intracystic PRL was 3000ng/mL in these two cases and > 40.000ng/mL in other prolactinomas, while one nonfunctioning adenoma, confirmed by ICQ, showed serum PRL of 48ng/mL and intracystic PRL of 34 ng/mL. Dosage of TSH, FSH and alpha subunit intracystic, performed in only one nonfunctioning adenoma, showed very high levels of these hormones. Our data suggest that the hormone dosage in material of cystic selar tumors may be helpful in differential diagnosis mainly when there is scarcely cellular material.

Disclosure: The authors have no relationships to disclose.

P50
Evaluation of Partial or Total Resistance to Cabergoline in Prolactinomas

Diez, S.M.; Ballarino, M.C.; Salazar, M.; Vallejos, J.; Stalldecker, G.

Hospital Pirovano, Caba, Argentina

Introduction: Most prolactinomas treated with cabergoline (CAB) are controlled with 1.5 – 2 mg/week. Some patients require a further increase of CAB dose to achieve normalization of prolactin (PRL) levels. Secondary resistance is rare. Discordance can occur between the reduction of both PRL levels and tumor size. Objective: To assess in our patients

a) Required dose of CAB to normalize PRL levels

b) Percentage of prolactinomas that do not respond to usual doses of CAB

c) Existence of secondary resistance

d) Discordance between the reduction of PRL levels and tumor shrinkage

Materials and Methods: sixty-two patients were evaluated: 25 microprolactinomas (23 women and 2 men) and 37 macroprolactinomas (22 women and 15 men), 13 of which were giant. Results: In microprolactinomas, Prl normalization was achieved in 22/25 patients, while 3/25 patients had lack of compliance. The average dose of CAB was 0.5 mg/week. Tumor shrinkage > 40% was observed in 16/25 patients, 8/25 remained stable, 1/25 had no control image. In no giant macroprolactinomas, PRL normalization was obtained in 19/24 patients, 2/24 patients had lack of compliance. The average dose of CAB was 1 mg/sem. One patient presented secondary resistance requiring surgery and radiotherapy. Tumor reduction > 25% was achieved in 15/24 patients, 8/24 remained stable, 1/24 had no control image. In giant macroprolactinomas, reduction of PRL levels >97% was obtained in all patients with a significant tumor shrinkage, average dose of CAB was 2 mg/week.

Conclusions: a) Conventional doses of CAB resulted in a normalization of PRL in all microprolactinomas and 75% of macroprolactinomas and giant prolactinomas that had compliance to treatment. A small group of giant prolactinomas required a higher dose of CAB; b) Discordance between PRL normalization and tumor shrinkage was observed in a small number of patients; c) Secondary resistance to CAB was an isolated event.

Disclosure: The authors have no relationships to disclose.

P51
Hemorrhagic and Non-Hemorrhagic Pituitary Apoplexy: A Cohort Study

Joseph H. Miller[1], Don E. McCormick[1], Esther Dupépé[1], Soni Srivastav[2], Daxa Patel[1], T. Brooks Vaughn III[2], and Kristen O. Riley[1]

[1]Division of Neurosurgery, University of Alabama at Birmingham; [2]Department of Medicine, Division Endocrinology, University of Alabama at Birmingham, Birmingham, Alabama, USA

Introduction: The diagnosis of pituitary apoplexy can be difficult as both the clinical presentation and radiographic appearance can be variable. There are subsets of patients that present with non-hemorrhagic pituitary apoplexy. Early identification and treatment of these patients is essential to prevent further visual decline, acute adrenal insufficiency, and poor outcomes.

Methods: Three hundred and eleven consecutive patients admitted with pituitary tumors were reviewed for evidence of pituitary apoplexy. Forty patients were found to have hemorrhagic or non-hemorrhagic pituitary apoplexy. A cohort statistical analysis was performed between the two groups. Patient demographics, comorbidities, initial clinical presentation, complications, and outcomes were analyzed for both groups.

Results: Patients with hemorrhagic (n = 23, 57.5%) and non-hemorrhagic (n=17, 42.5%) pituitary apoplexy were similar except the hemorrhagic cohort was older (mean age 51.5 versus 40.6, p=0.03) and more hypertensive (n=16, p=0.03). Presentation was similar between groups in terms of headache (n= 38, 95%: p=0.2), visual complaints (n=36, 90%: p = 0.8). There was no difference in visual acuity worse than 20/200 between the hemorrhagic (n=7, 20%) and non-hemorrhagic (n=9, 25.7%: p =0.4) cohort. Risks of post-operative complications were similar in both hemorrhagic (n=5: RR 1.13, 95% CI 0.59-2.1) and non-hemorrhagic cohorts (n=3: RR 0.84, 95% CI 0.31-2.3). Achievement of a good functional outcome as measured by modified Rankin scale better than 4 at last follow-up was not statistically different among cohorts (p = 0.74). No patient's vision worsened following surgery and 72.2% had improved visual acuity at discharge or last follow-up. Patients with post-apoplexy pituitary dysfunction were similar in the hemorrhagic (n =18, 48.7%) and non-hemorrhagic (n = 12, 32.4%: p = 0.41) cohorts.

Conclusions: Hemorrhagic and non-hemorrhagic pituitary apoplexy are similar clinical entities that require prompt surgical decompression of the optic apparatus and medical therapy aimed at treating acute adrenal insufficiency.

Disclosure: The authors have no relationships to disclose.

P52
Hemorrhagic and Non-Hemorrhagic Pituitary Apoplexy: A Radiographic Cohort Analysis

Joseph H. Miller[1], Don E. McCormick[1], Esther Dupépé[1], Soni Srivastav[2], Daxa Patel[1], T. Brooks Vaughn III[2], and Kristen O. Riley[1]

[1]Division of Neurosurgery, University of Alabama at Birmingham; [2]Department of Medicine, Division Endocrinology, University of Alabama at Birmingham, Birmingham, Alabama, USA

Introduction: Traditionally, pituitary apoplexy refers to a clinically significant acute hemorrhagic infarction of a pituitary adenoma. Patients suffering from apoplexy can present with headache, visual impairment, ophthalmoplegia, altered mental status, and death. The diagnosis can be difficult as the radiographic appearance can be variable. There are subsets of patients that present with non-hemorrhagic pituitary apoplexy. Early identification and treatment of these patients is essential to prevent further visual decline, acute adrenal insufficiency, and poor outcomes.

Methods: Three hundred and eleven consecutive patients admitted with pituitary tumors were retrospectively reviewed for clinical and radiographic evidence of pituitary apoplexy. Thirty-six operative patients and four non-operative patients were found to have hemorrhagic or non-hemorrhagic pituitary apoplexy. The determination of hemorrhagic apoplexy was based on radiographic assessment, intraoperative findings, and pathology demonstrating frank hemorrhage within a pituitary adenoma. A cohort statistical analysis was performed between the two groups using Chi Square, Fisher exact test, logistic regression, ANOVA, and t-test.

Results: Radiographic analysis demonstrated a significant difference in the hemorrhagic cohort's computed tomography (CT) finding of hyperdensity within the sella (n = 17, 48.5%, p = 0.02) and sellar Hounsfield units (mean 45 versus 38.1, p=0.05). Similarly, Hyperintensity on magnetic resonance imaging was more indicative of patients with hemorrhagic apoplexy according to T1 (p = 0.004), T2 (p = 0.004), and FLAIR (p = 0.04) imaging sequences. No difference was found in patterns of enhancement (p = 0.69) or restriction based on diffusion-weighted imaging (p = 0.54). Gradient echo (n=4) and susceptibility weighted imaging (n=1) effectively demonstrated hemorrhage within a pituitary adenoma.

Conclusions: The identification of hemorrhagic and non-hemorrhagic pituitary apoplexy can be improved through better understanding of the radiographic presentation. Prompt surgical decompression of the optic apparatus and medical therapy aimed at treating acute adrenal insufficiency can lead to improved patient outcomes.

Disclosure: The authors have no relationships to disclose.

P53
Impact of Selective Pituitary Gland Resection or Incision on Hormonal Function in Endonasal Tumor or Cyst Removal

Aaron R. Cutler[1], Amy Eisenberg[1], Pejman Cohan[1], Garni Barkhoudarian[1], Daniel F Kelly[1]

[1]Brain Tumor Center & Pituitary Disorders Program, John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, California, USA

Objective: In resection of pituitary adenomas or Rathke's cleft cysts (RCC), the anterior pituitary gland is often partially or completely obstructing transsphenoidal access to the lesion. In such cases, a gland incision and/or partial gland resection may be required to obtain adequate tumor/cyst exposure. We investigated the frequency with which this technique was performed in our practice and determined the associated risk of post-operative hypopituitarism.

Methods: All patients who underwent endoscopic-assisted or fully endoscopic removal of a pituitary adenoma or RCC between January 2011 and January 2013 (minimum 3 month follow-up) and had a gland incision or resection were included. Pre- and post-operative pituitary hormonal status was evaluated.

Results: Of 137 operations, an anterior gland incision or resection was performed in 41 cases (30%) in 39 patients. In 25 cases a vertical gland incision was made. In 16 cases a partial gland resection was performed including 8 partial hemi-hypophysectomies and 8 resections of thinned/ attenuated anterior gland draped over a large macroadenoma. Diagnoses included 32 pituitary adenomas (12 endocrine-inactive, 11 Cushing's, 7 prolactinomas, 2 acromegaly) and 9 RCCs. Of 33 patients with complete endocrine follow-up data, new permanent hypopituitarism occurred in 1 (3%) patient with a 3 cm macroadenoma who had partial gland resection; 2 patients experienced transient hyponatremia. Overall gland improvement occurred in 7/13 (54%) patients with pre-operative hopopituitarsim, including 5 with resolution of 1 axis or of stalk-effect hyperprolactinemia and 2 with resolution of 2 or more axes.

Conclusion: Pituitary gland incisions and partial gland resections are generally well-tolerated and can be performed when necessary to gain access to pituitary adenomas or RCCs. This technique, performed in 30% of cases, appears to minimize traction on normal pituitary gland during removal of large tumors or cyst and facilitates better visualization of microadenomas embedded in the anterior gland.

Disclosure: The authors have no relationships to disclose.

P54
Incidentally Discovered Pituitary Adenomas: Single-Center Experience In 225 Patients

Malchiodi E, Toini A, Dolci A, Ferrante E, Beck-Peccoz P, Spada A, Mantovani G

Department of Clinical Sciences and Community Health, University of Milan, Endocrinology and Diabetology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Introduction: Pituitary incidentalomas are lesions discovered on an imaging study performed for an unrelated reason. Their frequency varies among 0.2-38% and it is continuously increasing due to the development of neuroimaging techniques. Aim of the study is to investigate clinical and biochemical characteristics of 225 consecutive patients (68.5% female, mean age at diagnosis 46.5±18.0 years) with incidental pituitary adenoma (IPA) followed at our center from 1990 to present.

Methods: In all patients hormonal evaluation (basal antero-pituitary function, ACTH 250 mg stimulatory test, other dynamic tests when indicated) and pituitary imaging were performed at baseline, 6 months later and then annually if there was no other specific indication. 82 patients were also screened for subclinical hypercortisolism (cortisol after 1-mg overnight dexamethasone suppression test (1mg-DST), late-night salivary cortisol, 24-hours urinary free cortisol).

Results: At diagnosis 38.2% of patients had macroadenomas. One or more pituitary deficiencies were observed in 16.9% of cases (macro 27.0% vs micro 7.9%, P<0.05). Hyperprolactinemia (<100 ng/ml) was observed in 13.9% of patients (macro 15.5% vs micro 12.8%, P NS). Subclinical hypercortisolism was found in 4/82 (4.9%) patients studied (2 macroadenomas, 2 microadenomas). 119 patients had a follow-up longer than 12 months with a mean follow-up of 5.0 years. Radiological evaluation revealed a significant increase of tumor mass in 19/119 patients (16%, 13 macro vs 7 micro, P NS) and a reduction in 5.8% (all microadenomas). The volumetric increase occurred in 65% of patients during the first two years after diagnosis. Additional pituitary deficiencies were observed in 2.5% of patients during follow-up. Overall 19.1% of patients were treated with trans-sphenoidal adenomectomy owing to initial mass size or for their rapid increase.

Conclusions: Our data confirm that patients with IPA need for a close radiological and hormonal follow-up. In addition, we suggest exclusion of subclinical hypercortisolism in such patients.

Disclosure: The authors have no relationships to disclose.

P55
Initial Results of Stereotactic Linear Accelerator Based Irradiation for Pituitary Adenoma

Alice de Campos[1], Nina Rosa de Castro Musolino[2], Malebranche Berardo Carneiro da Cunha Neto[2], Evandro Cesar Souza[1], Sarah Campos Leal[1], Valter Angelo Sperling Cescato[2], Eduardo Weltman[1], Rosangela Correa Villar[1]

Instituto de Radiologia (INRAD) [1]Divisão de Neurocirurgia Funcional [2]Hospital das Clinicas, University of S.paulo, Medical School, Sao Paulo, Brazil

Radiotherapy is an efficient treatment for recurrent pituitary adenomas. Stereotactic linear accelerator based radiosurgery (LINAC) have been used in our Institution since 2008. Purpose: The purpose of this analysis was to evaluate the initial results in control rate after radiosurgery or fractionated stereotatic radiotherapy in pituitary adenoma.

Materials and methods: From september 2008 to July 2011, 36 patients were treated with fractionated stereotatic radiotherapy (FSR) or radiosurgery (RS) for pituitary adenomas. Tumor control was defined as normalization of basal hormonal levels and lack of progression of adenoma assessed by imaging studies. Follow-up included MRI and hormone evaluation.

Results: Twenty patients had nonfunctioning (NF) and sixteen had functional adenomas (acromegaly in ten and Cushing's disease in six cases). The median age was 44 years (range 17-72), with 29 females and 7 males. The median follow-up was 31 months (range 8-53). All patients received radiotherapy postoperatively for residual disease. All acromegaly patients were resistant to octreotide and cabergoline treatment. Mean total dose was 50,4Gy for fractionated stereotatic radiotherapy (n=25), and 20 Gy for radiosurgery (n=11: 3 with Cushing´s disease, 5 with acromegaly and 3 with NF). Twenty patients had stable disease based on MRI, while 15 had a reduction of tumor volume after 12 months. Regarding hormonal control, three of the six Cushing patients achieved normal urinary cortisol and midnight salivary cortisol levels after radiotherapy, one of them treated by RS. Although all patients were resistant to octreotide/cabergoline before radiotherapy, 3 of them obtained normal IGF-1 levels under medical treatment after irradiation and one patients with aggressive and invasive tumor showed normal IGF-1 levels without drug besides hypopituitarism.

Conclusion: Stereotatic radiotherapy is effective and safe in the treatment of pituitary adenomas to improve local control and can improve the hormonal control, with or without medical treatment.

Disclosure: The authors have no relationships to disclose.

P56

Isolated Langerhans Cell Histiocytosis of the Infundibular Stalk in an Adult with Central Diabetes Insipidus and Anterior Pituitary Dysfunction

Norra Kwong[1], Matthew L. Vestal [2], Kenneth M. Delosreyes[2], Edward R. Laws[2], Ursula B. Kaiser[1]

[1]Division of Endocrinology, Diabetes, and Hypertension, [2]Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts, USA

Introduction: Langerhans cell histiocytosis (LCH) is a rare, heterogeneous disorder characterized by clonal proliferation of pathologic Langerhans cells in various organs, predominantly seen in the pediatric population. Central diabetes insipidus (CDI) is the most common endocrinopathy in patients with LCH and is typically associated with multi-systemic disease. Here we present a rare case of isolated LCH of the infundibular stalk in an adult with CDI and anterior pituitary dysfunction.

Clinical case: A 42-year-old female presented with a three-month history of polydipsia and polyuria and was diagnosed with idiopathic CDI. MRI was negative. Six months later, she developed amenorrhea, and endocrinological examination revealed new onset of central hypogonadism, hyperprolactinemia, and central hypothyroidism. A repeat MRI showed a new infundibular stalk lesion. The patient underwent a diagnostic endoscopic transsphenoidal pituitary stalk biopsy. A discrete, well-circumscribed encapsulated mass was encountered during surgery, allowing its gross total resection. Pathology confirmed LCH. CDI has improved but not resolved, and she continues to require hormone replacement and experiences weight gain. Further comprehensive evaluation was negative for other cranial or extracranial lesions and close monitoring has remained negative for recurrence of disease.

Conclusion: Adult onset LCH with isolated pituitary involvement, such as our case, is rare and has been reported in only a few cases. It is important to recognize that a patient with LCH and CDI is at increased risk for anterior pituitary dysfunction and non-endocrine hypothalamic dysfunction such as weight gain, as demonstrated by our case. In addition, CDI in LCH is associated with subsequent development of systemic disease and warrants close follow-up. While the optimal treatment for isolated pituitary LCH is unknown, our case demonstrates that resection of a pituitary lesion through an endoscopic transsphenoidal approach can be used as a diagnostic tool as well as a possible treatment modality.

Disclosure: The authors have no relationships to disclose.

P57

Japan National Survey of Metastatic Pituitary Tumor – Preliminary Report on 200 Cases

M. Habu[1], S. Yunoue[1], S. Fujio[1], A. Teramoto[2], A. Shimatsu[3], K. Arita[3]

[1]Department of Neurosurgery, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan; [2]Department of Neurosurgery, Tokyo Rosai Hospital, Tokyo, Japan; [3]Department of Endocrinology and Metabolism, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

Background and Objective: The number of reports of metastatic (secondary) pituitary tumors has been increasing with progression of diagnostic and treatment skills for cancer patients. However, there were no nation-wide epidemiologic surveys or epidemiologic reviews about this topic. We have started a multi-institutional joint research in Japan to understand clinical features of metastatic pituitary tumors. Subjects and methods: We distributed 1069 closely monitored questionnaires to the institutions with members of the Japan Society for Hypothalamic and Pituitary Tumor, the Japan Society of Stereotactic Radiosurgery and the Japan Endocrine Society. As of end of 2012, we have identified 200 patients with metastatic pituitary tumor treated during the period from 1996 through 2012.

Results: The patients were predominantly male (111 vs. 89). The mean age of onset was 59.75 years ranging 26-86. The mean latency between the diagnosis of metastasis and the diagnosis of initial tumor was 744.5±884.4(SD) days in 58 reported patients. Diagnosis was pathologically in 65 patients (32.5%), by an imaging study and clinical course in 39 patients (19.5%), by the rise of the tumor marker in 14 patients (10.5%). Metastatic lesion was reported to be found earlier than the initial sites in 8 patients. 92 cases (46%) were diagnosed within one year of the primary tumor diagnosis. More than 10 years have elapsed since primary lesion was diagnosed in 10 cases. The main sites of primary lesions included lung (38.5%), breast (21.5%), kidney (7%), colon (6.1%), liver (4%), stomach (2%), thyroid (2%), and unknown (4%). The frequent symptoms were diabetes insipidus (28%), general fatigue (27%) and extra-ocular muscle palsy (22%), nausea or vomiting (13%), coma (8%) and seizure (2%). Patients with primary tumor had been well controlled when diagnosed metastases is only 30%. Surgery is 22% of the patients, 81% who received radiation therapy. Primary cause of death was a worsening of the primary tumor (42%). Mortality due to worsening of metastases is 24% except for the head; death from metastatic pituitary tumor was 10%. The mean survival time was 11.7 months, in which the 3-year survival rate was 33.3%. The median survival time tended to be longer in stereotactic radiation group than in conventional radiation group; 11.6 vs. 8.8 months, but not statistically significant (p=0.26, Logrank).

CONCLUSION: The Japanese Survey for Metastatic Pituitary Tumor is accumulating data on metastatic pituitary tumor, which must be conducive for early diagnosis and proper treatment of this pathologic entity.

Disclosure: The authors have no relationships to disclose.

P58

Natural History and Management of Incidentally Found Asymptomatic Pituitary Cystic Lesion Mimicking Rathke's Cleft Cyst

Atsushi Tominaga, Yasuyuki Kinoshita, Satoshi Usui, and Kaoru Kurisu

Department of Neurosurgery, Hiroshima University Hospital, Hiroshima, Japan

We surveyed the natural history of asymptomatic pituitary cystic lesion (APCL) and evaluate its management.

Subjects: Of 135 patients with cystic pituitary lesions analyzed, 86 (group AS) had no symptoms and 49 (group H) had headaches at the first visit, and 77 and 38 patients were followed-up, respectively. Nine AS and 11 H patients underwent transsphenoidal surgery. Follow-up time ranged from 0.5 to 23 (median: 4.1) years.

Methods: We monitored the pituitary function and cyst size at 0, 3, 6 months, and thereafter every year after the first visit. Statistical analysis was performed using the Kaplan-Meyer method. Results: 1) The cumulative cyst-shrinkage free rates for groups AS and H at 5 and 10 years follow-up were 69% and 77%, and 69% and 60%, respectively. 2) The cumulative cyst-enlargement free rates for groups AS and H at 5 and 10 years follow up were 93% and 100%, and 89% and 100%, respectively. Four patients developed symptoms during the follow-up period. 3) In patients with cyst-intensity changes on MRI, the cumulative cyst-shrinkage rates were significantly ($p<0.001$) higher than those with unchanged cyst intensity. 4) Four patients (3.5%) had severe growth hormone deficiency (GHD) and 13 patients (11%) had hyperprolactinemia at first admission. 5) Eight (40%) of 20 operated patients had cyst recurrence. None developed hypopituitarism after surgery.

Conclusions: 1) APCLs are rarely symptomatic. 2) In the natural history of APSL, ca. 40% of patients indicated shrinkage. 3) A few patients (3.5%) with APCL may have severe GHD. 4) Due to the high recurrence rate of APCL, surgery is not the easy option.

Disclosure: The authors have no relationships to disclose.

P59

Non-Functioning Pituitary Adenoma Hyperuptake at 68Ga-DOTANOC PET/CT

Piacentini S.[1], Perotti G.[2], Lugli F.[1], Iacovazzo D.[1], Bianchi A.[1], Giampietro A.[1], Giovannini E.[2], Treglia G.[2], Rufini V.[2], Maira G.[3], De Marinis L.[1]

[1]Endocrinology, [2]Nuclear Medicine, [3]Neurosurgery, Catholic University, Policlinico "A. Gemelli", Rome, Italy

Introduction: pituitary adenomas are among the most common brain tumors, with a prevalence ranging from 78 to 94 cases per 100,000 inhabitants, 68% of which are macroadenomas. Case series have documented that up to 20% of macroadenomas grow significantly during follow-up. Patient with non-functioning pituitary adenoma (NFPA), if symptomatic, are generally referred for transsphenoidal surgical approach, with proved low morbidity and mortality and an overall recurrence rate of about 5%. High expression of somatostatin receptors SST2 and SST5 in NFPA (70-90%) represents the rationale of using radiolabelled somatostatin analogues (SSAs) in the diagnosis and in case of tumor relapse; moreover there is some evidence for the possible use of somatostatin analogues in the medical treatment of NFPAs. Indium-111-pentetreotide scintigraphy has been often used to diagnose NFPA relapse, with a sensibility between 80-90%.

Materials and methods: a 53-year old male patient was referred to our Institution in April 2011 with onset of severe headache and visual field defects. An MRI showed a voluminous expansive process at the sellar and suprasellar region, with bilateral cavernous sinus involvement and extension into the third ventricle, compression of the brain stem and dislocation of the optic chiasm. The patient underwent partial removal of the lesion through transsphenoidal approach. Histological examination showed null cell pituitary adenoma with a Ki-67 of 3%. After ten months a follow-up MRI showed the presence of the residual pituitary adenoma localized at the sellar-suprasellar region. The patient underwent brain 68Ga-DOTANOC PET/CT.

Results: brain 68Ga-DOTANOC PET/CT showed intense focal uptake corresponding to the lesion visualized at the MRI. Therefore, SSAs treatment was started, with further evidence of disease stabilization.

Conclusion: 68Ga-DOTANOC PET/CT can be a useful tool not only in confirming the diagnosis of residual NFPA but could also play a role in selecting patients for medical treatment with SSAs.

Disclosure: The authors have no relationships to disclose.

P60
Pituitary Adenomas in a Series of Patients with Clinical Multiple Endocrine Neoplasia Type 1 (MEN1)

Iacovazzo D.1, Lugli F.[1], Giampietro A.[1], Veltri F.[1], Bianchi A.[1], Lucci-Cordisco E.[2], Capoluongo E.[3], Maira G.[4], Neri G.[2], De Marinis L.[1]

[1]Endocrinology, [2]Medical Genetics, [3]Clinical Biochemistry, [4]Neurosurgery, Catholic University, Policlinico "A. Gemelli", Rome, Italy

Introduction: MEN1 is defined clinically as the occurrence of two or more primary MEN1 tumor types (pituitary adenomas, primary hyperparathyroidism and gastroenteropancreatic neuroendocrine tumors - GEP NETs). The prevalence of MEN1 is approximately 2 x 100'000. MEN1 has been associated to germline mutations of MEN1, a gene encoding for a 610-amino acid protein called menin. MEN1 mutations can be identified in 70-90% of clinical MEN1 patients.

Materials and methods: we describe a series of 20 patients (12 F, 8 M) affected by pituitary adenomas associated with hyperparathyroidism and/or GEP NETs, analysing their clinical features. All patients underwent mutational analysis of MEN1 by direct sequencing; MLPA has been performed when no mutations were found.

Results: MEN1 mutations have been found only in 25% of patients (group A), while in the remaining patients no mutations have been identified, even with the MLPA technique (group B). The mean age of all patients at diagnosis of pituitary adenoma is 44.6 years (SD 13.9 years). Patients in group A presented with pituitary adenoma at a significant younger age (34 years) compared to patients in group B (48 years; $p<0.05$). Prolactinomas were prevalent in group A (80%), while, in group B, GH-secreting adenomas were more commonly found (53%), followed by NFPAs (27%) and prolactinomas (20%). In group A, 80% of patients have been diagnosed with GEP NETs (mostly duodenal gastrinomas and non functioning pancreatic NETs), while, in group B, this occurred only in 13% of patients.

Conclusion: in our series, MEN1 mutations have been identified in a small percentage of cases. Patients carrying a mutation present with specific clinical features: younger age, higher rate of prolactinomas and associated GEP NETs. The high proportion of patients without mutations suggests that other genes may be involved or that the association between these endocrine tumors can be accidental.

Disclosure: The authors have no relationships to disclose.

P61
TSH Secreting Pituitary Tumor (Thyrotropinoma): Presentation of Five Cases

Pignatta A, Tolosa C, Loto M, Manavela M, Abbati Gonzalez S, Danilowicz K

Service of Endocrinology, Hospital San Juan Bautista, Catamarca; Service of Endocrinology, Hospital Británico; and Division of Endocrinology and Neurosurgery, Hospital de Clínicas ¨José de San Martín¨, Buenos Aires, Argentina

Thyrotropinomas are the less frequent adenomas (1%). We describe 5 cases. Case 1: 23-year-old man, with sudden atrial fibrillation and goiter. TSH:4,2uUI/ml, T4:14,8ug/dl(to 12,5), FT4:2,2ng/dl(to 1,9), T3:170ng/dl(to 180), FT3:7,8pg/ml(to 4,6) and flat TRH test. MRI revealed a macroadenoma. Euthyroidism was reached with octreotide while methimazol failed. He underwent transsphenoidal surgery (TSS). Immunohistochemistry was positive for TSH. After surgery, TSH was suppressed for 30 days and he was free of disease for 4 years. Case 2: 41-year-old woman with hypertension and goiter. TSH:3,21uUI/ml, T4:16,9ug/dl, FT4:2,2ng/dl, T3:245ng/dl and flat TRH test. On MRI a microadenoma was diagnosed and reached 10,8 mm 2 years later. TSS was performed. Immunohistochemical staining was positive for TSH and GH. One month after surgery, she presented suppressed TSH. Case 3: 53-year-old man with loss of libido and hypertension. TSH:9,1uUI/ml, FT4:1,79ng/dl, T3:164ng/dl. Thyroid ultrasound (US) showed a goiter. MRI showed a macroadenoma. TSS was performed, the adenoma was positive for TSH and GH. The patient developed primary hipothyroidism. Case 4: 36-year-old woman with clinical hyperthyroidism. Thyroid US showed a goiter. TSH:3,76uUI/ml, T4:13,2ug/dl, fT4:2,3ng/dl, T3:247ng/dl and TRH test was flat. MRI showed an adenoma of 10 mm. She underwent TSS. Immunohistochemical staining was positive for TSH and GH. TSH was suppressed for 45 days. She is free of disease for the last 7 years. Case 5: 49-year-old man, with decreased libido and occasional headaches. On MRI an invasive macroadenoma was found. TSH:14,4 uUI/ml, T4:14,8 ug/dl T4L:4,1ng/dl. Octreotide was started and he was lost on follow-up.

Conclusions: We present these cases due to their low prevalence. We emphasize that clinical presentation was variable. We can speculate on the secretion of a less biologically active TSH. 5/5 showed non suppressed TSH. 3/5 presented a macrodenoma. 3/5 showed TSH suppression one week after surgery which might be considered as a criteria of cure. 4/4 operated patients cured.

Disclosure: The authors have no relationships to disclose.

P62

Xanthogranuloma, Rathke's Cyst, and Childhood Craniopharyngioma – Results of Prospective Multinational Studies of Children And Adolescents with Rare Sellar Malformations

Hermann L. Müller[1*], Ursel Gebhard[1], Andreas Faldum[2], Monika Warmuth-Metz[3], Torsten Pietsch[4], Gabriele Calaminus[5]

[1]Dep. of Pediatrics, Klinikum Oldenburg, Oldenburg; [2]Institute for Biometry and Clinical Research, University of Münster, Münster; [3]Dep. of Neuroradiology, University Hospital, Würzburg; [4]Institute for Neuropathology, University Hospital, Bonn; [5]Dep. of Pediatrics, University Hospital, Münster; Germany. on behalf of the study committee KRANIOPHARYNGEOM 2000/2007

Background: Craniopharyngioma (CP), Rathke's cyst (RC) and xanthogra¬nuloma (XG) are closely related rare sellar masses, which share common embryogenic origin. Treatment strategies in children lack consensus, especially in terms of surgical and radiooncological treatment options. Objective: To study clinical manifestations and treatment-related outco¬me in RC, XG, and CP patients. Patients and methods: Multicentre surveillance trial. Inclusion crite¬ria were: 1) histological diagnosis of CP, XG or RC; 2) diagnosis.

Main Outcome: Overall survival, event-free survival (OS, EFS), quality of life (QoL). 14 RC, 14 XG, and 117 CP patients were included in the study. Results: 5-year OS rates are 1.00±0.00 in RC and XG; 0.97±0.02 in CP.5-year EFS are 0.85±0.10 in RC, 1.00±0.00 in XG, and 0.50±0.05 in CP. Surgical resection of XG results in complete remission without recurren¬ce. Recurrences occur in RC (14%) and CR (59%), but can be efficiently treated by irradiation, reoperation, and/or intracystic treatment. Severe hypothalamic sequelae such as obesity and others effecting QoL are pre¬dominant in CP due to pre-surgical involvement (59%) and post-surgical lesions (44%) of posterior hypothalamic structures. Centres with lower neurosurgery patient load use more radical surgical approaches to treat CP, resulting in higher rates of obesity and reduced QoL. In spite of 46% anterior hypothalamic involvement, severe obesity is not encountered in XG.

Conclusions: Treatment of choice in XG and RC is radical surgery. In CP involving hypothalamic structures, less radical surgical approaches preserving hypothalamic integrity are recommended. Due to frequent relapses, regular imaging during follow-up is recommended for CP and RC. Treatment of patients with sellar masses should be confined to expe¬rienced multidisciplinary teams. Due to the rareness of the diseases, international scientific collaboration (i.e. international trials) is recommended in order to achieve reliable results based on evaluation of larger cohorts.

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Index by Title

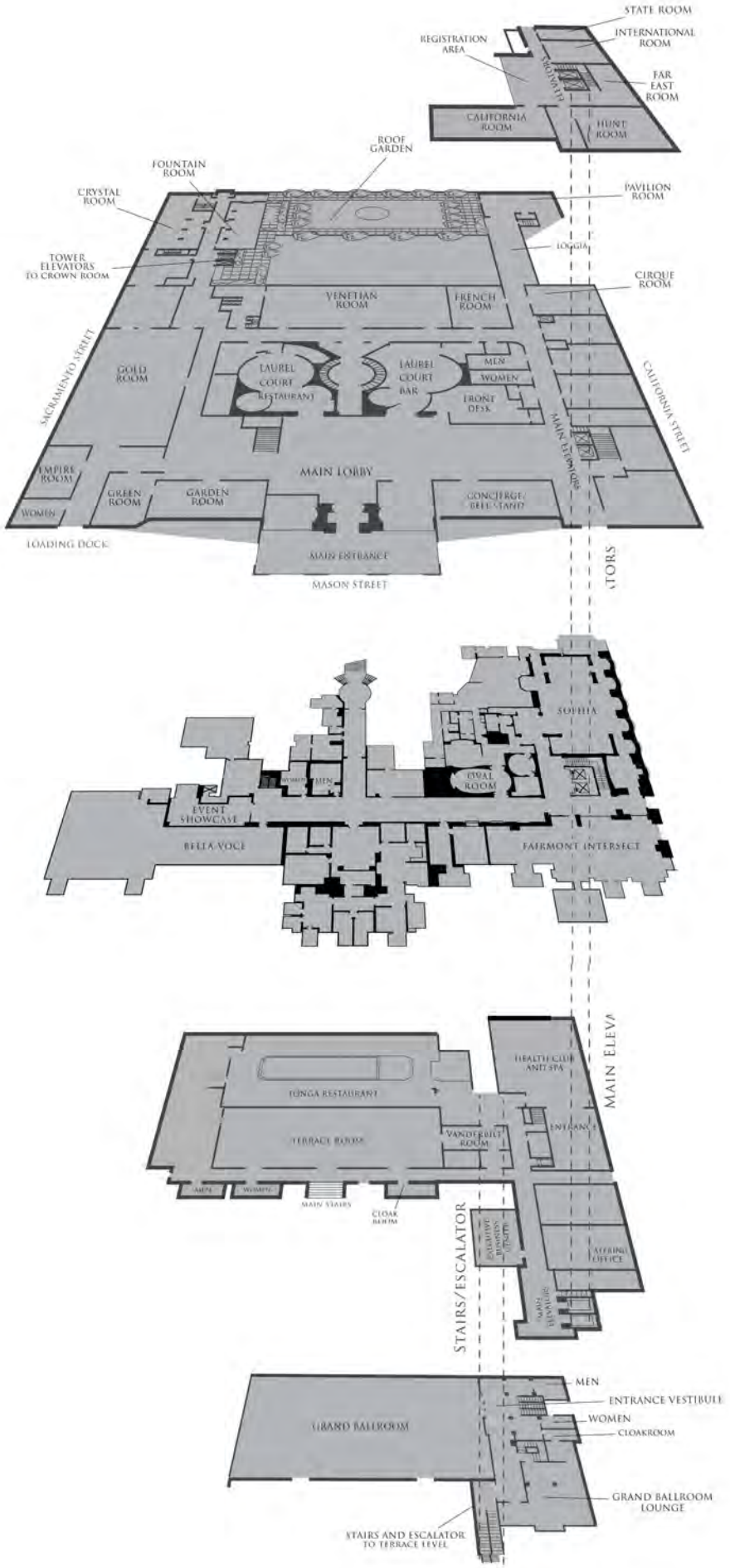
Author	Title	Page	Poster Number
Fainstein Day, P.	Evolution of a Silent GH Pituitary Adenoma (PA) to an Aggressive GH Secreting Tumor After Pregnancy	39	5
Boguszewski, C.	From Anorexia Nervosa to Nelson Syndrome: An Atypical Presentation of a Cushing's Disease	47	21
Waters, M.	GH/IGF-1 and Cancer	14	Invited Lecture
Miller, J.	Hemorrhagic and Non-Hemorrhagic Pituitary Apoplexy: A Cohort Study	63	51
Miller, J.	Hemorrhagic and Non-Hemorrhagic Pituitary Apoplexy: A Radiographic Cohort Analysis	64	52
Klein, A.	High Frequency of Headache in Patients with Hyperprolactinemia	58	40
Fusco, A.	HMGA as a Driver of Pituitary Tumorigenesis	7	Invited Lecture
Newell-Price, J.	How to Differentiate Central from Ectopic ACTH-Dependent Cushing's Syndrome	23	Invited Lecture
Caturegli, P.	Immunomodulation and Lymphocytic Hypophysitis	14	Invited Lecture
Cutler, A.	Impact of Selective Pituitary Gland Resection or Incision on Hormonal Function in Endonasal Tumor or Cyst Removal	64	53
Malchiodi, E.	Incidentally Discovered Pituitary Adenomas: Single-Center Experience in 225 Patients	65	54
Mamelak, A.	Influence of Tumor Volume and Cavernous Sinus Invasion on Hormone Levels and Remission Following Endoscopic Transsphenoidal Surgery for Acromegaly	39	6
de Campos, A.	Initial Results of Stereotactic Linear Accelerator Based Irradiation for Pituitary Adenoma	65	55
Kwong, N.	Isolated Langerhans Cell Histiocytosis of the Infundibular Stalk in an Adult with Central Diabetes Insipidus and Anterior Pituitary Dysfunction	66	56
Klose, M.	iSYS Versus Immulite: A Clinical Comparison of Assay Specific Cut-Offs for the Insulin Tolerance and Pyridostigmin GHRH Test	49	24
Habu, M.	Japan National Survey of Metastatic Pituitary Tumor – Preliminary Report On 200 Cases	66	57
Elias, P.	Late Night Salivary Cortisol (LNSF) Versus 24-H Urinary Free Cortisol (UFC) in the Diagnosis of Cushing's Syndrome (CS): A Concomitant Samples Collection Study During Three Consecutive Days	47	22
Sterkenburg, A.	Long-Term Weight Development and Psychosocial Status in Childhood Craniopharyngioma Patients	54	33
Manavela, M.	Management of Pregnant Acromegalic Patients in LA: A Retrospective Study	40	7
Kinoshita, Y.	Masked Hyperprolactinemia: Tumor-Derived Factors Inhibiting Prolactin Secretion Caused by Pituitary-Stalk Damage	58	41
Drouin, J.	Mechanisms for Pituitary Cell Fate Choice	13	Invited Lecture
Bollerslev, J.	Mechanisms for Somatostatin Analog Resistance – Clinical Aspects	9	Invited Lecture
Farrell, W.	Mechanisms Underlying Treatment Resistance	9	Invited Lecture
Smith, S.	Medical Training Does Not Influence the Ability to Perform Successful Injections of Somatuline® Depot (SD; Lanreotide)	40	8
Ayuk, J.; Bonert, V.; Chanson, P.; Strasburger, C.	Medical Treatment of Acromegaly	34	Invited Lecture
Tritos, N.	Metabolic and Bone Benefits of Adult GH Replacement	19	Invited Lecture
Mallea-Gil, S.	Microprolactinomas Evolution After Menopause	59	42
Knosp, E.	MRI and Surgery in Aggressive Pituitary Adenomas	27	Invited Lecture
Zatelli, M.	mTOR Mediates IGF-1 Proliferative Effects in a Rat Pituitary GH/PRL Secreting Pituitary Adenoma Cell Line	45	18
Tominaga, A.	Natural History and Management of Incidentally Found Asymptomatic Pituitary Cystic Lesion Mimicking Rathke's Cleft Cyst	67	58
Hoffman, A.	No Long-Term Weight Reduction After Gastric Banding (Lagb) in Obese Patients with Craniopharyngioma Involving Hypothalamic Structures - Experiences from Kraniopharyngeom 2000/2007	44	16
Piacentini, S.	Non-Functioning Pituitary Adenoma Hyperuptake at 68Ga-DOTANOC PET/CT	67	59

Author	Title	Page	Poster Number
Katakami, H.	Novel and Highly Sensitive EIAs for the Differential Diagnosis (DDx) Between Cushing's Disease (CD) and Ectopic ACTH Syndrome (EAS)	30	Hot Topic
Swearingen, B.	Options After Initial Surgical Failure: If At First You Don't Succeed…	33	Invited Lecture
Karppinen, A.	Outcome of Microscopic Versus Endoscopic Surgery for Nonfunctional Pituitary Adenomas at The Helsinki University Central Hospital	55	34
Grossman, A.	Peri-operative Management of Patients with Cushing's Disease	24	Invited Lecture
Dantas, R.	Physical Activities in Daily Life and Functional Capacity Compared to Disease Activity Control in Acromegalic Patients: Impact in Self-Reported Quality of Life	41	9
Iacovazzo, D.	Pituitary Adenomas in a Series of Patients with Clinical Multiple Endocrine Neoplasia Type 1 (MEN1)	68	60
Mukherjee, K.	Pituitary Dysfunction After Aneurysmal Subarachnoid Hemorrhage. Is There a Difference Between Middle Cerebral Artery and Anterior Communicating Artery Aneurysms?	55	35
Bondanelli, M.	Predictive Role of Inflammatory Cytokines and Neurotrophic Factors Plasma Levels on Pituitary Function After Ischemic and Hemorrhagic Stroke	56	36
Webb, S.	Pregnancy and Cushing's Syndrome: A Preliminary Report	24	Invited Lecture
Nunes, V.	Presurgical Somatostatin Analogues Versus Direct Surgery in the Treatment of Newly Diagnosed Acromegalic Patients: A Systematic Review of Randomized Studies	41	10
Mota, J.	Profile of Acromegalic Patients in Use of Pegvisomant in a Tertiary Hospital in Brazil	42	11
Robbins, R.	Recombinant Human TSH – 20 Years of Experience in Man	15	Invited Lecture
Gül, N.	Recovery From Hypogonadotrophıc Hypogonadısm in a Young Woman wıth Perıpartum Hypophysıtıs After Steroıd Replacement Therapy	56	37
Kwancharoen, R.	Second Attempt to Withdraw Cabergoline in Hyperprolactinemia	59	43
Zhou, C.	STAT3 Induces Growth Hormone Exression in Pituitary Somatotroph Cells	29	Hot Topic
Tkatch, J.	Successful Reversion of Cardiomyopathy Following Treatment with Somatostatin Analogs in a Patient with Acromegaly	42	12
Brzana, J.	Symptomatic Perioperative Venous Thromboembolic Events in Patients with Cushing's Disease: A Call For Prophylaxis	48	23
McCormack, A.	Temozolomide and Aggressive Pituitary Tumours: Longer-Term Follow-Up	30	Hot Topic
Ho, K.	The Promise of Growth Hormone: Separating Fact from Fiction	18	Invited Lecture
Gül, N.	Three Cases wıth Hypogonadısm, Polyurıa and Polydıpsıa as Presentıng Manıfestatıons of Neurosarcoıdosıs	57	38
Horseman, N.	Transgenic Prolactin Cancer Models	13	Invited Lecture
Locatelli, M.	Transphenoidal Surgery for GH Pituitary Adenomas: An Anatomical Study	43	13
Thompson, C.	Traumatic Brain Injury and Hypopituitarism	22	Invited Lecture
Pignatta, A.	TSH Secreting Pituitary Tumor (Thyrotropinoma): Presentation of Five Cases	68	61
Oruk, G.	Two Successive Pregnancies with Diabetes İnsipidus	57	39
Fleseriu, M.	What's Next After Failed Pituitary Surgery for Cushing's Disease: Medical Therapeutic Approaches	33	Invited Lecture
Dutta, P.	Which is Better Test for Diagnosing Acromegaly in Patients with Co-Existing Diabetes Mellitus: GH, IGF-1 or IGFBP-3?	43	14
Dattani, M.	Wnt/beta-catenin Signaling in Craniopharyngioma	11	Invited Lecture
Müller, H.	Xanthogranuloma, Rathke's Cyst, and Childhood Craniopharyngioma – Results of Prospective Multinational Studies of Children And Adolescents with Rare Sellar Malformations	69	62

Index by Author

Author	Title	Page	Poster Number
Gallardo, W.	An Observational, Comparative Trial in Patients with Active Acromegaly Receiving a New Long-acting Octreotide Formulation Who Were Previously Treated with the Original Octreotide Formulation (Sandostating LAR)	37	1
Gregerson, K.	Completely Humanizing Prolactin Rescues Infertility in Prolactin Knockout Mice	29	Hot Topic
Grossman, A.	Peri-operative Management of Patients with Cushing's Disease	24	Invited Lecture
Gül, N.	Recovery From Hypogonadotrophıc Hypogonadısm in a Young Woman wıth Perıpartum Hypophysıtıs After Steroıd Replacement Therapy	56	37
Gül, N.	Three Cases wıth Hypogonadısm, Polyurıa and Polydıpsıa as Presentıng Manıfestatıons of Neurosarcoıdosıs	57	38
Habu, M.	Endocrinologic Function in Nonfunctioning Pituitary Adenomas With Predominantly Exophytic Growth	53	31
Habu, M.	Japan National Survey of Metastatic Pituitary Tumor – Preliminary Report On 200 Cases	66	57
Heaton, A.	Effects of an Amino Acid Based hGH Secretagogue on Triiodothyronine	50	25
Ho, K.	The Promise of Growth Hormone: Separating Fact from Fiction	18	Invited Lecture
Hoffman, A.	No Long-Term Weight Reduction After Gastric Banding (Lagb) in Obese Patients with Craniopharyngioma Involving Hypothalamic Structures - Experiences from Kraniopharyngeom 2000/2007	44	16
Horseman, N.	Transgenic Prolactin Cancer Models	13	Invited Lecture
Iacovazzo, D.	Pituitary Adenomas in a Series of Patients with Clinical Multiple Endocrine Neoplasia Type 1 (MEN1)	68	60
Ignacio, D.	Estrogen Regulates Exercise-Induced Pituitary Type 1 Deiodinase Increase and Growth Hormone Secretion	50	26
Jung, K.	Different Cut-Off Values of the Insulin Tolerance Test, the High Dose Short Synacthen Test (250 µg) and the Low Dose Short Synacthen Test (1 µg) in Assessing Adrenal Insufficiency	46	20
Karavitaki, N.	Aggressive Pituitary Tumors: Clinical Markers	26	Invited Lecture
Karppinen, A.	Outcome of Microscopic Versus Endoscopic Surgery for Nonfunctional Pituitary Adenomas at The Helsinki University Central Hospital	55	34
Katakami, H.	Novel and Highly Sensitive EIAs for the Differential Diagnosis (DDx) Between Cushing's Disease (CD) and Ectopic ACTH Syndrome (EAS)	30	Hot Topic
Kinoshita, Y.	Masked Hyperprolactinemia: Tumor-Derived Factors Inhibiting Prolactin Secretion Caused by Pituitary-Stalk Damage	58	41
Klein, A.	High Frequency of Headache in Patients with Hyperprolactinemia	58	40
Klose, M.	iSYS Versus Immulite: A Clinical Comparison of Assay Specific Cut-Offs for the Insulin Tolerance and Pyridostigmin GHRH Test	49	24
Knosp, E.	MRI and Surgery in Aggressive Pituitary Adenomas	27	Invited Lecture
Kovacs, K.	Aggressive Pituitary Adenomas	25	Invited Lecture
Kwancharoen, R.	Second Attempt to Withdraw Cabergoline in Hyperprolactinemia	59	43
Kwong, N.	Isolated Langerhans Cell Histiocytosis of the Infundibular Stalk in an Adult with Central Diabetes Insipidus and Anterior Pituitary Dysfunction	66	56
Locatelli, M.	Transphenoidal Surgery for GH Pituitary Adenomas: An Anatomical Study	43	13
Malchiodi, E.	Incidentally Discovered Pituitary Adenomas: Single-Center Experience in 225 Patients	65	54
Mallea-Gil, S.	Microprolactinomas Evolution After Menopause	59	42
Mamelak, A.	Influence of Tumor Volume and Cavernous Sinus Invasion on Hormone Levels and Remission Following Endoscopic Transsphenoidal Surgery for Acromegaly	39	6
Manavela, M.	Management of Pregnant Acromegalic Patients in LA: A Retrospective Study	40	7
McCormack, A.	Temozolomide and Aggressive Pituitary Tumours: Longer-Term Follow-Up	30	Hot Topic
Miller, J.	Hemorrhagic and Non-Hemorrhagic Pituitary Apoplexy: A Cohort Study	63	51
Miller, J.	Hemorrhagic and Non-Hemorrhagic Pituitary Apoplexy: A Radiographic Cohort Analysis	64	52

Author	Title	Page	Poster Number
Mota, J.	Profile of Acromegalic Patients in Use of Pegvisomant in a Tertiary Hospital in Brazil	42	11
Mukherjee, K.	Pituitary Dysfunction After Aneurysmal Subarachnoid Hemorrhage. Is There a Difference Between Middle Cerebral Artery and Anterior Communicating Artery Aneurysms?	55	35
Müller, H.	Diencepephalic Syndrome Before Diagnosis of Childhood Craniopharyngioma - Results of Multinational Studies on 485 Long-Term Survivors After Childhood Craniopharyngioma	44	15
Müller, H.	Xanthogranuloma, Rathke's Cyst, and Childhood Craniopharyngioma – Results of Prospective Multinational Studies of Children And Adolescents with Rare Sellar Malformations	69	62
Muraoka, T.	Clinical Characteristics of 15 Patients with Hypophysitis	52	29
Newell-Price, J.	How to Differentiate Central from Ectopic ACTH-Dependent Cushing's Syndrome	23	Invited Lecture
Nunes, V.	Presurgical Somatostatin Analogues Versus Direct Surgery in the Treatment of Newly Diagnosed Acromegalic Patients: A Systematic Review of Randomized Studies	41	10
Oruk, G.	Two Successive Pregnancies with Diabetes İnsipidus	57	39
Petersons, C.	Acute Effect of Increasing Glucocorticoid Replacement Dose on Insulin Sensitivity and Cardiovascular Risk in Patients with Adrenocorticotrophin Deficiency	51	27
Piacentini, S.	Non-Functioning Pituitary Adenoma Hyperuptake at 68Ga-DOTANOC PET/CT	67	59
Pignatta, A.	TSH Secreting Pituitary Tumor (Thyrotropinoma): Presentation of Five Cases	68	61
Raff, H.	Cushing Diagnosis – New Options	17	Invited Lecture
Rizo, I.	Evaluation of Postoperative Day 1 and 5 Morning Serum Cortisol After Transsphenoidal Resection of Pituitary Adenoma to Predict Hypothalamic-Pituitary-Adrenal Function	54	32
Robbins, R.	Recombinant Human TSH – 20 Years of Experience in Man	15	Invited Lecture
Schlechte, J.	Dopamine Agonist Withdrawal - When and How?	17	Invited Lecture
Simsek, Y.	Comparıson of Low Dose ACTH and Glucagon Stimulatıon Tests with Insulin Tolerance Test	53	30
Smith, S.	Medical Training Does Not Influence the Ability to Perform Successful Injections of Somatuline® Depot (SD; Lanreotide)	40	8
Sterkenburg, A.	Long-Term Weight Development and Psychosocial Status in Childhood Craniopharyngioma Patients	54	33
Swearingen, B.	Options After Initial Surgical Failure: If At First You Don't Succeed…	33	Invited Lecture
Thompson, C.	Traumatic Brain Injury and Hypopituitarism	22	Invited Lecture
Tkatch, J.	Successful Reversion of Cardiomyopathy Following Treatment with Somatostatin Analogs in a Patient with Acromegaly	42	12
Tominaga, A.	Natural History and Management of Incidentally Found Asymptomatic Pituitary Cystic Lesion Mimicking Rathke's Cleft Cyst	67	58
Tritos, N.	Metabolic and Bone Benefits of Adult GH Replacement	19	Invited Lecture
Trouillas, J.	A New Prognostic Clinicopathological Classification of Pituitary Endocrine Tumors: A Multicentric Case-Control Study of 410 Patients with 8 Years Post-Operative Follow-Up	60	45
Vitali, E.	cAMP Exerts Proliferative and Anti-proliferative Effects by Activating Both cAMP-dependent Protein Kinase A (PKA) and Exchange Proteins Directly Activated by cAMP (Epac) in Different Pituitary Cells Types	45	17
Wass, J.	Craniopharyngioma – Management Challenges	18	Invited Lecture
Waters, M.	GH/IGF-1 and Cancer	14	Invited Lecture
Webb, S.	Pregnancy and Cushing's Syndrome: A Preliminary Report	24	Invited Lecture
Zatelli, M.	mTOR Mediates IGF-1 Proliferative Effects in a Rat Pituitary GH/PRL Secreting Pituitary Adenoma Cell Line	45	18
Zhou, C.	STAT3 Induces Growth Hormone Exression in Pituitary Somatotroph Cells	29	Hot Topic



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