

THE PITUITARY SOCIETY
presents the

11th ELEVENTH
INTERNATIONAL
PITUITARY CONGRESS

JUNE 13 – 15, 2009



June 13 – 15, 2009

Washington, DC

Immediately following Endo 2009

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PROGRAM AND ABSTRACTS

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Welcome

Dear Colleague,

The 11th International Pituitary Congress will present an exciting group of member and guest international experts in pituitary problems. It will include distinguished 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 the participants and speakers.

As is customary, this meeting follows the ENDO 2009 Meeting, which means that the Eleventh International Pituitary Congress will begin on the evening of Saturday, June 13th and end the afternoon of Monday, June 15th. The meeting will be held at The Omni Shoreham Hotel in Washington, DC. It is a lovely venue that will encourage excellent science and great fun. Anyone who has attended one of our Congresses can attest to the beautiful and elegant surroundings, wonderful science, and excellent entertainment.

This guide provides details of the scientific program as well as all the abstracts selected for Hot Topics and poster presentations. Please take note of our corporate partners who are supporting both our educational sessions and social events. We gratefully acknowledge their continued support. Welcome again to two days of excellent science and companionship!

The Program Organizing Committee



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Symposium Schedule

SATURDAY, JUNE 13, 2009

- 12:00 NOON – 6:00 PM Welcome and Registration
- 6:30 – 7:00 Plenary Opening Lecture - Supported by an unrestricted educational grant from Pfizer
Endocrinology of Aging *Steven W. J. Lamberts (The Netherlands)*
- 7:00 – 8:00 Poster Presentations
- 8:30 **OPENING RECEPTION** - Supported by Ipsen

SUNDAY, JUNE 14, 2009

8:00 AM Continental Breakfast

Pediatric Neuroendocrinology

Supported by an unrestricted educational grant from Genentech

Chair: Sally Radovick (USA)

- 9:00 **Pituitary Transcription Factors** *Sally Radovick (USA)*
- 9:20 **Metabolic Consequences of Primary vs. Secondary IGF Deficiency in Children and Adults** *Madhusmita Misra (USA)*

Neuroendocrinology of Body Composition

Supported by an unrestricted educational grant from Genentech

Chair: Ken Ho (Australia)

- 9:40 **Obesity and Antipsychotic Medications** *John Newcomer (USA)*
- 10:00 **Hypothalamic Regulation of Bone** *Paul Baldock (Australia)*
- 10:20 **Body Composition-Neuroendocrine Interrelationships in Anorexia Nervosa and Obesity** *Karen Miller (USA)*
- 10:40 Coffee Break

Neuroendocrinology of Competitive Sports

Chair: Christian Strasburger (Germany)

- 11:00 **Neuroendocrine Consequences of Competitive Sports: An Overview** *Fabio Lanfranco (Italy)*
- 11:20 **Detection of Growth Hormone Doping by the Marker-strategy** *Ken Ho (Australia)*
- 11:40 **Differential Immunoassays for Detection of Growth Hormone Doping by the Isoform-strategy** *Martin Bidlingmaier (Germany)*

Symposium Schedule

12:00 NOON-1:00 PM **MEET THE PROFESSOR SEMINARS** (Lunch Provided)

MP1 Prolactinomas

Janet Schlechte (USA)

MP2 Acromegaly Primary Therapy: Yes or No?

Supported by an unrestricted educational grant from Novartis

Debate Chair: Marcello Bronstein (Brazil)

Brooke Swearingen (USA) and Michael Sheppard (UK)

MP3 Adult GH Deficiency

Michael Thorner (USA)

MP4 Pitfalls of Cortisol Replacement

Paul Stewart (UK)

MP5 Approach to Pubertal Delay

Ursula Kaiser (USA)

Neuroendocrinology & Cardiovascular Disease

Supported by an unrestricted educational grant from Novo Nordisk

Chair: David Clemmons (USA)

1:00 PM **Changes in Insulin Sensitivity and Glucose Sensing in GHRelin Receptor Knockout Mice** *Roy Smith (USA)*

1:20 **GHRelin and the Regulation of Peripheral Metabolic Function** *Ezio Ghigo (Italy)*

GH Axis

Supported by an unrestricted educational grant from Novo Nordisk

Chair: John Kopchick (USA)

1:40 **The Breast as a GH Axis Target** *David L. Kleinberg (USA)*

2:00 **Pituitary Somatotrophic Cell Networks** *Iain Robinson (UK)*

2:20 **GH and Cancer: Animal Models** *Steven Swanson (USA)*

2:40 **GH and Cancer Risk: Epidemiologic Update** *Michael Pollak (Canada)*

3:00 Coffee Break

ACTH Axis

Supported by an unrestricted educational grant from Novartis

Chair: Lynnette Nieman (USA)

3:20 **Vasopressin Antagonists** *Joseph Verbalis (USA)*

3:40 **Pathogenesis of Cushing's Disease** *Jacques Drouin (Canada)*

4:00 **Nelson's Syndrome** *Xavier Bertagna (France)*

4:30 Poster Presentations

7:30 **GALA DINNER** - Supported by Ipsen

Symposium Schedule

MONDAY, JUNE 15, 2009

8:00 AM Continental Breakfast

Genetic Syndromes

Supported by an unrestricted educational grant from Novartis

Chair: Monica Gadelha (Brazil)

8:30 **Central Precocious Puberty: The Roles of Kisspeptin and GPR-54 Protein** Ana Claudia Latronico (Brazil)

8:50 **Carney Complex: Pathogenesis of GH and Prolactin Hypersecretion** Lawrence Kirschner (USA)

9:10 **Familial Isolated Pituitary Adenomas: Clinical and Genetic Features** Lawrence A. Frohman (USA)

9:30 Coffee Break

Pituitary Tumor Biology

Supported by an unrestricted educational grant from Novartis

Chair: Eduardo Arzt (Argentina)

9:50 **Regulation of the Number of Somatotropes** Clara Alvarez (Spain)

10:10 **Epigenetically Silenced Genes in Pituitary Tumors** William Farrell (UK)

10:30 **Cytokine Regulation of Pituitary Growth** Günter Stalla (Germany)

Hypopituitarism

Supported by an unrestricted educational grant from Novo Nordisk

Chair: Mary Lee Vance (USA)

10:50 **Congenital Hypopituitarism** Simon J. Rhodes (USA)

11:10 **Treatment of Hypopituitarism: Is Growth Hormone Really Necessary for Adults?** Christian Strasburger (Germany) and Ariel Barkan (USA)

11:30 **Treatment of Hypopituitarism: What is an Optimal Glucocorticoid Regimen for Bone and Heart Protection?** John Newell-Price (UK)

Luncheon and Awards Presentations

Chair: David L. Kleinberg (USA)

12:00 Noon **Presidential Address**

12:15 **Travel Grant Awards**

12:30 **The Novartis Pituitary Society Lifetime Achievement Award**

The Pituitary Society Outstanding Young Investigator Award

Chairs: Paolo Beck-Peccoz (Italy) and David Clemmons (USA)

1:30 Supported by Eli Lilly & Co.

The Pituitary Society Outstanding Young Investigator Award and Presentation

Everolimus Blocks IGF-1 Effects on Human Non Functioning Pituitary Adenomas In Vitro

Maria Chiara Zatelli (Italy)

Symposium Schedule

Hot Topics

Supported by an unrestricted educational grant from Novartis

Chairs: Paolo Beck-Peccoz (Italy) and David Clemmons (USA)

- 2:00 **Corticotroph Pituitary Tumor Transforming Gene Overexpression Induces Hypercortisolism, Glucose Intolerance and Hepatic Steatosis: A Zebrafish Transgenic Model for Cushing's Disease** *Ning-Ai Liu (USA)*
- 2:15 **STAT3 Induces Pituitary Tumor Transforming Gene (PTTG) Expression** *Cuiqi Zhou (USA)*
- 2:30 **A Mouse Model of Adult-onset, Isolated, GH-deficiency (AOiGHD) Reveals Long-term Reductions in Gh/Igf1 Improve Insulin Sensitivity But Impair the Compensatory Rise in Insulin Observed with Diet-induced Obesity** *Rhonda Kineman (USA)*
- 2:45 **High Prevalence of Vertebral Fractures Despite Normal Bone Mineral Density in Patients with Long Term Controlled Acromegaly** *Nienke Biermasz (The Netherlands)*
- 3:00 Congress Adjourns

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ABSTRACTS
PLENARY OPENING LECTURE

Endocrinology of Aging

Steven WJ Lamberts¹ and Joseph AMJ Janssen¹

¹Erasmus Medical Centre, ²Department of Medicine, Rotterdam, The Netherlands

Aging is associated with a progressive decrease in growth hormone (GH) secretion and insulin-like growth factor I (IGF-I) concentrations. Current insights suggest that this decreased activity of the GH/IGF-I-axis, together with estrogen deficiency after menopause and a reduction in bioavailable testosterone in men, contribute to the development of sarcopenia, abdominal obesity, osteopenia, insulin resistance, type 2 diabetes, and cardiovascular disease. The normal range of serum IGF-I is very wide. In a study in mono- and dizygotic twins we found that heritability of serum IGF-I levels was very high, higher than that of IGF-BP3, DHEAS, cortisol or IGF-BP1 levels. It has been suggested that at least 38% of the interindividual variability in circulating IGF-I levels is genetically determined. GH, insulin, nutrition, age, but especially also the currently available immunoassays contribute to the intra-individual variation of IGF-I measurements which can between assays be as high as 25%. Despite these problems population studies in the elderly suggest that IGF-I levels in the upper limit of normal roughly increase the risk of prostate cancer, and levels in the lower limit predict type 2 diabetes and cardiovascular disease.

Recently we developed an assay for the measurement of circulating IGF-I bioactivity, using an IGF-I-specific kinase receptor activation assay (KIRA), which theoretically has the advantage that it measures net effects of IGF-binding proteins on IGF-I receptor activation. Although time-consuming this measurement has a variation coefficient of 7% only.

In a prospective study in 376 old men (73-94 yrs), 170 men (45%) died during the follow-up of nearly 9 years. Immunologically measured total or free IGF-I did not predict death. However, survival of participants in the highest quartile of IGF-I-bioactivity was significantly better than in those in the lowest quartile. This suggests that relatively high circulating IGF-I bioactivity in elderly men is associated with extended survival. This also suggests that immuno- and bioassayable IGF-I differ with respect to their influence in the aging process.

We extensively studied the IGF-I gene for common variation (polymorphisms). Preliminary data support our previous findings that a polymorphic region composed of multiple cytosine adenosine (CA)-repeats about 1 Kb upstream of the promoter region of the IGF-I gene strongly influences circulating immuno-reactive, but not bio-active IGF-I levels. This IGF-I gene polymorphism is associated with the age-related decline of serum immuno-IGF-I concentrations, body height, as well as the risk for type 2 diabetes mellitus, and cardiovascular disease (myocardial infarction and heart failure), while it protects against prostate cancer.

Conclusions: It is presently unknown whether IGF-I influences human longevity. There seems a pathophysiologically important difference in immuno- and bio-assayable IGF-I. Genetic variability in the gene(s) responsible for IGF-I regulation plays a role in the risk for diabetes and cardiovascular morbidity during the aging process.

ABSTRACTS
YOUNG INVESTIGATOR AWARD

YIA

Everolimus Blocks IGF-1 Effects on Human Non Functioning Pituitary Adenomas In Vitro

Maria Chiara Zatelli¹, Mariella Minoia¹, Carlo Filieri¹, Federico Tagliati¹, Mattia Buratto¹, Davide Casini¹, Maria Rosaria Ambrosio¹, Ettore degli Uberti¹

¹Section of Endocrinology, University of Ferrara, Dept. of Biomedical Sciences and Advanced Therapies, Ferrara, Italy

Non-functioning pituitary adenomas (NFA) are orphan of an effective medical therapy. Everolimus (RAD001), an immunosuppressant drug, has antineoplastic activity in human cancers, including endocrine tumors. Our aim is to study the effects of RAD001 on cell viability and apoptosis in 22 human NFA in primary culture. Cells were treated with 10 nM - 1 mM RAD001, 50 nM IGF-1, and/or 10 nM SOM230 (a somatostatin receptor multiligand). After 48 h, cell viability was evaluated with a colorimetric method, and apoptosis with caspase 3/7 and caspase 9 assays. Cell viability was significantly and dose-dependently reduced by RAD001 in 13 out of 22 cultures (-15 to -35%), which blocked the promoting effects of IGF-1. SOM230 significantly reduced cell viability (-20%), but did not enhance RAD001 effects. Caspase 3/7 activity was significantly induced by RAD001 (+25%) which blocked the inhibitory effects of IGF-1. SOM230 did not influence caspase 3/7 activity and did not enhance RAD001 effects. Caspase 9 activity was not modified by any treatment. Our data demonstrate that RAD001 inhibits cell viability in selected NFA, by inducing caspase 3/7 activity with a mechanism involving IGF-1 signaling, which is not enhanced by somatostatin receptor ligands. Our results suggest that RAD001 acts as a pro-apoptotic stimulus, inducing the extrinsic pathway, and might represent a possible medical treatment aiming at controlling pituitary adenoma growth.

Disclosure: RAD001 was provided by Novartis.

ABSTRACTS
HOT TOPICS

HT1

Corticotroph Pituitary Tumor Transforming Gene Overexpression Induces Hypercortisolism, Glucose Intolerance and Hepatic Steatosis: A Zebrafish Transgenic Model for Cushing's Disease

Ning-Ai Liu¹, Hong Jiang¹, Haigan Huang¹, Song-Guang Ren¹, Xue-Mo Fan¹, Anat Ben-Shlomo¹, Shuo Lin¹, Shlomo Melmed¹

¹*Cedars-Sinai Research Institute, Los Angeles, CA, United States*

Pituitary tumor transforming gene (PTTG) encodes securin that regulates G1/S and G2/M phase transition. Murine models have exploited PTTG down-regulation as an approach to suppress pituitary tumorigenesis. PTTG deletion or overexpression in GH-secreting cells promotes p53/p21-dependent senescence, contributing to the benign propensity of pituitary tumors. However, mechanisms for PTTG-mediated pituitary tumorigenesis remain unclear. **OBJECTIVE:** Develop a germline transgenic zebrafish model with corticotroph-directed PTTG overexpression. **METHODS/RESULTS:** The zebrafish genome contains a single copy gene encoding a protein that shares high homology with human PTTG. We generated transgenic zebrafish expressing zPttg driven by Pomc promoter. Corticotroph Tg:Pomc-Pttg expression was confirmed by RNA WIH. Tg:Pomc-Pttg expression was inhibited by dexamethasone and up-regulated by RU486. POMC cell expansion was evident in 4 day old transgenic embryos compared to controls. Tg:Pomc-Pttg fish showed increased interrenal steroidogenic cells, and cortisol levels ($1.4 \pm 0.4 \mu\text{g/L/mg}$ vs. $1.0 \pm 0.4 \mu\text{g/L/mg}$) by 3 months. ~20% of homozygote transgenic zebrafish developed neoplastic-appearing pituitary cells with a high nuclear/cytoplasmic ratio, distinct nucleoli and small to moderate amounts of basophilic cytoplasm with strong ACTH staining and morphologically resembling human ACTH-secreting adenomas. Transgenic zebrafish showed increased fasting blood glucose ($96 \pm 9 \text{ mg/dL}$ vs. $65 \pm 10 \text{ mg/dL}$, $p < 0.0000001$), and post-prandial blood glucose levels, vs. controls. Over 50% of Tg:Pomc-Pttg fish developed hepatic steatosis by 20 months. **CONCLUSIONS:** Corticotroph-targeted PTTG transgenic zebrafish manifest a phenotype mimicking human hypercortisolism due to Cushing's disease. Zebrafish PTTG function is conserved for pituitary tumorigenesis, as for mammals. Given the utility of zebrafish for large-scale, phenotype-based genetic and pharmacological studies, this model of Cushing's disease provides a helpful tool for understanding mechanisms underlying development of Cushing's disease, and identifying small molecule POMC repressors.

Disclosure: Nothing to disclose.

HT2

STAT3 Induces Pituitary Tumor Transforming Gene (PTTG) Expression

Cuiqi Zhou¹, Kolja Wawrowsky¹, Serguei Bannykh², Shlomo Melmed¹

¹*Cedars-Sinai Medical Center, Medicine, Los Angeles, California, United States*, ²*Cedars-Sinai Medical Center, Pathology, Los Angeles, California, United States*

Pituitary tumor transforming gene (PTTG), a securin protein, maintains chromosomal stability and mediates tumorigenesis. PTTG is abundantly overexpressed in multiple human tumors, but mechanisms regulating tumor PTTG overexpression are still elusive. As EGF induces PTTG expression in TtT/GF folliculostellate cells, and STAT3 is required for cytokine and growth factor responses, we investigated STAT3 regulation of PTTG.

STAT3 and PTTG were concordantly overexpressed in 50 human pituitary tumor specimens (56% and 62%; $P < 0.01$, Pearson χ^2 test; Institutional Review Board approved) as assessed by confocal immunofluorescence. Notably, only 12% of pituitary tumors were detected increased STAT3 phosphorylation. EGF and IL-6 treatment does-dependently increased STAT3 phosphorylation and PTTG expression in HCT116 cells. STAT3 specifically bound to the PTTG promoter (-2000 to -3000 nt) as assessed by chromatin immunoprecipitation, implying that PTTG may act as a STAT3 target. We constructed wild type STAT3, constitutively activated STAT3 (STAT3-C) and dominant negative STAT3 (STAT3-DN) plasmids, and respectively selected stable transfectants in malignant HCT116 and benign pituitary AtT20 cells. STAT3 transfection induced PTTG expression up to 2-fold in both HCT116 and AtT20 cells as assessed by western blot and real-time PCR. The induction was enhanced by STAT3-C (3-fold) and totally abrogated by STAT3-DN (0.7-fold). Stable STAT3 overexpression promoted in vitro colony formation in both HCT116 and AtT20 transfectants, and colony formation was strongly attenuated by PTTG RNAi (~50%, $P < 0.01$). Furthermore, elevated STAT3 expression or activation increased HCT116 cell migration and invasion up to 5-fold as measured by in vitro cell migration and invasion assays, whereas cell mobility was completely abolished by STAT3-DN (>90%). Knockdown of PTTG expression by RNAi strongly suppressed STAT3-induced cell migration and invasion by up to 80% in both STAT3 and STAT3-C transfectants.

These results elucidate a molecular mechanism for tumor PTTG abundance, whereby STAT3 upregulation and/or activation induces PTTG expression to facilitate tumor formation and metastasis. These findings further elucidate PTTG actions in tumor progression and indicate that PTTG is a potential therapeutic target for abrogating growth of endocrine tumors.

Disclosure: Nothing to disclose

HT3

A Mouse Model of Adult-onset, Isolated, GH-deficiency (AOiGHD) Reveals Long-term Reductions in Gh/Igf1 Improve Insulin Sensitivity but Impair the Compensatory Rise in Insulin Observed with Diet-induced Obesity

Raul M. Luque^{1,2,3}, Qing Lin^{1, 2}, Jose Cordoba-Chacon³, Thorsten Buch⁴, Ari Waisman⁵, Hugo Vankelecom⁶, Rhonda D. Kineman^{1,2}

¹Jesse Brown Veterans Affairs Medical Center, Chicago, Illinois, United States, ²University of Illinois at Chicago, Department of Medicine, Chicago, Illinois, United States, ³University of Cordoba, Department of Cell Biology, Physiology and Immunology, Cordoba, Spain, ⁴University of Zurich, Experimental Neuroimmunology, Zurich, Switzerland, ⁵Johannes Gutenberg-University, Medical Department, Mainz, Germany, ⁶University of Leuven, Department of Molecular Cell Biology, Leuven, Belgium

The decline in GH that occurs with age and obesity may contribute to metabolic syndrome initiation/progression. To test this hypothesis we developed a model of AOiGHD using the Cre/loxP system by breeding rGh promoter-Cre recombinase mice (Cre) to inducible diphtheria toxin receptor mice (iDTR). Somatotropes of Cre+,iDTR+ express DTR. In the absence of the toxin, pituitary/somatotrope morphology and function is normal compared to WT or Cre-,iDTR+ controls. When adult Cre+,iDTR+ mice are treated with DT, somatotropes are selectively destroyed and circulating Gh/Igf1 reduced (AOiGHD) compared to DT-treated Cre-,iDTR+ mice (Gh-INTACT). AOiGHD fed standard chow (17% kcal from fat) do not differ in body weight, but have larger fat depots, compared to Gh-INTACT. AOiGHD show improved response to ITT and have reduced fed insulin and glucose, compared to Gh-INTACT, while response to GTT is unchanged. To mimic a more "western" diet, Cre+,iDTR+ and Cre-,iDTR+ mice (3 months) were treated with DT (osmotic pumps, 6ng/h for 7d) and fed either a low fat (LF,10%) or high fat (HF,45%) diet. At 8 months, the respiratory quotient (VCO₂/VO₂, as determined by indirect calorimetry) of AOiGHD was significantly elevated compared to Gh-INTACT and this difference was more pronounced during LF feeding in the absorptive state. These results indicate AOiGHD utilize more carbohydrates for cellular metabolism, consistent with improved insulin sensitivity. The response to GTT at 9 months did not differ between LF-fed AOiGHD and Gh-INTACT, however glucose clearance in HF-fed AOiGHD was impaired and fasting insulin reduced, relative to HF-fed Gh-INTACT. Using Igf1 as a surrogate marker of GHD, fasting Igf1 was positively correlated with insulin within diet. Taken together these results suggest that lowering adult Gh/Igf1 improves insulin sensitivity, but Gh/Igf1 is required to maintain ss-cell function.

(Grant support was provided by VA Merit and NIA 5621AG031465 to RDK and RYC-2007-00186 to RML)

Disclosure: Nothing to disclose

HT4

High Prevalence of Vertebral Fractures Despite Normal Bone Mineral Density in Patients with Long Term Controlled Acromegaly

Nienke Biermasz¹, Moniek Wassenaar¹, Neveen Hamdy¹, Ferdinand Roelfsema¹, Marcel Stokkel¹, Margreet Kloppenburg³, Herman Kroon², Hans Romijn¹, Alberto Pereira Arias¹

¹Leiden University Medical Center (LUMC), The Netherlands, ²LUMC, Radiology, The Netherlands, ³LUMC, Rheumatology, The Netherlands

Objective: To establish the prevalence of osteoporosis, vertebral, and non-vertebral fractures in acromegaly patients with long-term controlled disease (mean 14 years) and to study factors potentially influencing fracture risk.

Design: Cross-sectional study

Methods: We studied quantitative morphometric vertebral fractures, non-vertebral fractures, bone mineral density (BMD), and biochemical markers of bone turnover in 89 patients (46% male) with a mean age of 58.2 years. A baseline BMD 7 year earlier was available in 48 patients.

Results: The prevalence of vertebral fractures was 59% (men 64%, women 54%). No difference was found between patients with controlled disease for 2-14 years (57%) and for >14 years (59%). 55% had ≥1 fracture at the thoracic spine and 18% had ≥1 fracture at the lumbar spine (LS) level. Mean number per patient was 3.4±0.3 (range 1-8). Mean LS-BMD was 1.01±0.02 g/cm², and mean Z-score +0.45±0.20. Mean total hip BMD was 0.88±0.02 g/cm², and mean Z-score +0.46±0.10. BMD, markers for bone turnover, and acromegalic disease characteristics did not differ between patients with or without fractures. There was a gender difference in the prevalence of vertebral fractures with more men than women with one or more documented vertebral fracture (56 vs. 44%; p=0.02). Hypogonadal men had a higher prevalence of vertebral fractures (86%) than eugonadal (19%) or hypogonadal (49%) women (p<0.05). BMD in ongoing controlled acromegaly was stable over 7 years.

Conclusion: Patients with acromegaly have a high prevalence of vertebral fractures despite normal BMD measurements. In view of the significant morbidity and mortality associated with vertebral fractures and the inability of BMD to predict fracture risk, we advocate the inclusion of lateral conventional radiographs of the spine in the screening of patients with acromegaly.

Disclosure: Nothing to disclose

ABSTRACTS
ACROMEGALY

P1

Cytokeratin Expression Pattern and Response to Octreotide in Acromegalic Patients

Alessandra Fusco¹, Laura Tilaro¹, Libero Lauriola², Flora Veltri¹, Linda Tartaglione¹, Vincenzo Cimino¹, Francesco Doglietto³, Antonio Bianchi¹, Eduardo M Fernandez³, Carmelo Anile³, Giulio Maira³, Alfredo Pontecorvi¹, Laura De Marinis¹

¹Catholic University, Endocrinology, largo "A. Gemelli" Rome, Italy, ²Catholic University, Pathology, largo "A. Gemelli", Rome, Italy, ³Catholic University, Neurosurgery, largo "A. Gemelli" Rome, Italy

Introduction: The GH-secreting pituitary adenomas can be distinguished in type 1 and 2 based on the immunohistochemical cytokeratin expression pattern. The type 1 adenoma is characterized by a "dot-like" cytokeratin distribution, whereas the type 2 shows a diffuse cytokeratin distribution. The type 1 adenoma displays a more aggressive clinical behaviour compared to the type 2, in that it appears at a younger age and is characterized by higher tumor size and recurrence rate after surgery.

Aim of the study: To evaluate the response to octreotide in a large group of acromegalic patients not cured by surgery according to hormonal values at diagnosis and the cytokeratin expression pattern from the adenoma.

Materials and methods: This was a retrospective study which included 50 acromegalic patients not cured by surgery and treated with long-acting octreotide. Based on the clinical characteristics, GH nadir after OGTT and IGF-I levels, the patients were classified as either controlled or uncontrolled by octreotide (maximal dose 30mg/monthly). Tumor samples from each patient were submitted to immunohistochemistry with the CAM5.2 antibody (cytokeratin 8 and 18).

Results: 36 out of 50 patients were considered controlled by octreotide therapy (C; 72%), whereas 14 patients were considered uncontrolled (NC; 28%). Age at diagnosis was similar between the two groups. Mean pre-surgical GH nadir and IGF-I levels were higher in the NC group compared to C group. Concerning the cytokeratin expression, the dot-like pattern was found in 14 tumors (38%) from the C group and in 10 tumors (72%) from the NC group ($p < 0.05$). The diffuse pattern was present in 22 cases (62%) from the C group and in 4 cases (28%) from NC group ($p < 0.05$).

Conclusions: The dot-like pattern from a GH-secreting pituitary adenoma has a lower probability to respond to octreotide. The cytokeratin expression pattern from the adenoma may have important implications for a better therapeutic strategy in acromegaly.

Disclosure: Nothing to disclose

P2

Treatment of Prognathism in Acromegalic Patient: Case Report

Sema Yarman¹, Turkey

¹Istanbul Medical Faculty, Internal Medicine, Endocrinology and Metabolism, Istanbul/Capa, Turkey

Acromegaly is a chronic and slowly developing endocrinopathy and the health consequences of untreated acromegaly are severely impairing the quality of life. Control of clinical signs and symptoms seem to have a positive impact on psychological condition. We report a case about a 33 year old man who admitted to a dentist due to severe mandibular prominence and masticatory dysfunction. After then, he was referred to plastic surgery. Due to his acromegalic features, the patient was sent to us for endocrinologic evaluation at 1998. On the basis of laboratory and radiological evidence, he was diagnosed as acromegaly. After a transcranial operation his laboratory examination showed that the disease was active in 1999. Subsequently radiotherapy and medical therapy (OCT-LAR, 20 mg/monthly) was undertaken. Elevated GH and IGF-1 levels had been controlled by OCT-LAR for about 8 years. During follow-up period, his prognathism and masticatory dysfunction has not progressed but he suffered from this abnormalities and insisted for surgical correction. Therefore, we decided to correct the mandibular deformity. The surgical procedures and the postoperative course of the patient was uneventful. The results of facial appearance and occlusion were excellent. Possibly due to the effect of radiation therapy, he has been free of medical treatment since the last six months with normal IGF-1 and GH levels and partial empty sella. In conclusion, this case demonstrates the importance of the treatment of acromegaly before any orthodontic therapy is recommended, and this problem should be managed with a multidisciplinary approach when the disease activity is under control.

Disclosure: Nothing to disclose

P3

Safety of Long-term Combined Therapy with Somatostatin Analogues (SA) and Cabergoline (CAB) on Cardiac Valve in Acromegaly: An Echocardiography Study

Renata S Auriemma¹, Maurizio Galderisi², Mariano Galdiero¹, Ludovica F.S Grasso¹, Maria C De Martino¹, Monica De Leo¹, Gaetano Lombardi¹, Annamaria Colao¹, Rosario Pivonello¹

¹Federico II University, Department of Clinical and Molecular Endocrinology and Oncology, Naples, Italy, ²Federico II University, Department of Clinical and Experimental Medicine, Naples, Italy

To evaluate the prevalence of cardiac valve insufficiency after 12-month treatment with SA and CAB in acromegalic patients partially responsive to SA. GH, IGF-1 and echocardiography were performed in twenty-four patients at diagnosis, after therapy with SA and 12 months after CAB plus SA in order to evaluate ejection fraction (EF) and mitralic (M), tricuspidal (T), aortic (A) and pulmonary (P) regurgitation (R). CAB was added at the initial dose of 1 mg weekly, then increased up to 0.5 mg daily after three months on the basis of GH and IGF-1. SA treatment induced a significant decrease, but not normalization, in GH ($p < 0.001$) and IGF-1 levels ($p < 0.001$). After CAB plus SA GH ($p < 0.001$) and IGF-1 ($p = 0.002$) levels were normalized. EF was increased ($p < 0.001$) after SA, whereas CAB plus SA induced only slight, but not significant, further increase in EF. At the study entry, patients showed: mild MR in 85%, moderate MR in 4.2%, mild TR in 41.2%, moderate TR in 8.3%, mild AR 8.3%, moderate AR in 8.3% and mild PR in 16.6% of patients, respectively. After SA, mild MR was decreased ($p = 0.002$), as well as moderate TR ($p < 0.05$) and mild PR ($p < 0.05$). After CAB plus SA, mild MR and AR were furtherly reduced ($p < 0.001$ and $p < 0.01$ respectively), whereas mild PR was increased ($p < 0.05$). However, none of the patients developed pulmonary hypertension either during SA monotherapy or after combined treatment with SA and CAB. CAB addition to SA improves the biochemical control of acromegaly in patients partially responsive to SA. Valve dysfunctions seem to be improved after the addition of CAB. A long-term combined treatment with SA and CAB is effective and safe in acromegaly.

Disclosure: Nothing to disclose

P4

Histopathological Changes in Pituitary Adenoma Treated with Growth Hormone Receptor Antagonist for 4 Years in a Patient with Octreotide-resistant Acromegaly

Satoko Shimazu^{1,2}, Akira Shimatsu^{1,2}, Toshiaki Sano³, Shozo Yamada⁴, Takuya Nakakuki⁵, Takeshi Usui^{1,2}, Tetsuya Yagami^{1,2}, Mitsuhide Naruse^{1,2}, Testuya Tsukahara⁵

¹NHO Kyoto Medical Center, Dept Endocrinol Metab, Kyoto, Japan, ²NHO Kyoto Medical Center, Clin Res Inst, Kyoto, Japan, ³Univ Tokushima Grad Sch, Dept Human Pathol, Tokushima, Japan, ⁴Toranomon Hosp, Dept Hypothalamo-Pituitary Surg, Tokyo, Japan, ⁵NHO Kyoto Medical Center, Dept Neurosurg, Kyoto, Japan

Growth hormone receptor antagonist (GHRA), pegvisomant, has been introduced for the treatment of acromegaly. Few reports have focused on the histological changes induced by GHRA. We describe here a case of octreotide-resistant acromegaly who had been treated with pegvisomant for four years and compare the histopathological findings of adenoma specimens before and after GHRA. Thirty-one year-old woman was referred to our hospital because of pituitary tumor. She had complained of numbness of the fingers, headache and excessive sweating for two years. MRI showed macroadenoma invaded into the right cavernous sinus. Serum GH and IGF-1 levels were 26.4 ng/ml and 858 ng/ml, respectively. Octreotide therapy failed to decrease her GH levels. She had undergone first transsphenoidal surgery with incomplete resection. Pegvisomant was introduced with normalization of IGF-1. After four years, she undertook the second transnasal endoscopic surgery. After surgery, oral glucose administration suppressed her GH levels less than 0.21 ng/ml with marginally elevated serum IGF-1 levels (360 ng/ml). She has been followed without additional therapy. Specimens from two separate pituitary operations were stained for pituitary hormones, markers of cellular proliferation, and cytokeratin. The first specimen was chromophobic and immunoreactive for GH with ring enhancement. In the tumor exposed to pegvisomant, cells became smaller and immunoreactivities of GH were reduced with Golgi pattern. Ki-67 labelling index did not show any significant changes. The differences between two specimens were the appearance of keratin-positive intracytoplasmic fibrous bodies. In conclusion, we could not confirm the previous report by Drake et al. that showed increased proliferation markers after pegvisomant treatment. GHR antagonism may result in sparsely granulated phenotype with fibrous bodies in somatotroph adenoma.

Disclosure: This study was in part supported by the research grants from the Foundation for Growth Science in Japan and from the Ministry of Health, Labour and Welfare, Japan.

P5

Effects of 6 Months of GH Administration on Cardiac Function in Patients with Previously Treated Acromegaly and GH Deficiency

Pouneh Fazeli¹, Tamara Wexler¹, Ronen Durst², David McCarty², Michael Picard², Karen Miller¹, Anne Klibanski¹

¹Massachusetts General Hospital and Harvard Medical School, Neuroendocrine Unit, Boston, MA, United States

²Massachusetts General Hospital and Harvard Medical School, Cardiac Unit, Boston, MA, United States

Although growth hormone replacement is prescribed for hypopituitary patients with growth hormone deficiency (GHD), it is not routinely used to treat GHD following cure of acromegaly. Alterations in cardiac structure and function are observed in both acromegaly and GHD. In active acromegaly, cardiac dysfunction and increased left ventricular (LV) mass occur, whereas in GHD decreased LV mass and diastolic dysfunction have been reported. We investigated GH administration in patients with GHD after definitive therapy (surgery and/or radiation) for acromegaly and assessed changes in LV mass and diastolic function as part of a 6-month randomized, single-blind, placebo-controlled study. GHD was defined as peak GH of <5 ng/ml on a GHRH-arginine test or a low IGF-1 level with 3 other pituitary deficiencies. We studied 12 individuals not receiving somatostatin analogues or pegvisomant. Diastolic function, as measured by deceleration time (DT), and LV mass corrected for body surface area (LV mass/BSA) were measured at baseline and 6 months. There was no worsening of diastolic function in patients treated with GH or placebo as measured by DT. Mean LV mass/BSA was normal at 71.7 ± 5.8 g/m² in females (n=5) and 95.8 ± 6.7 g/m² in males (n=7) at baseline. All but one subject had normal LV mass/BSA measurements at baseline. Five subjects in each group had 6-month LV mass/BSA measurements. There was a trend toward an increase in % change of LV mass in the GH-treated group vs. the placebo group (placebo: $1.4 \pm 5.1\%$ versus GH: $14.9 \pm 4.6\%$, p=0.08). One subject randomized to GH progressed from a normal to a mildly increased LV mass/BSA measurement and one progressed from a normal to a moderately increased measurement; the one subject with a mildly increased LV mass/BSA measurement at baseline remained unchanged after 6 months of GH. One subject randomized to placebo also progressed from a normal to a mildly increased LV mass/BSA. These findings suggest that GH treatment for GHD after cure from acromegaly may affect LV mass and does not worsen diastolic function. Further studies are needed to determine the long-term benefits and risks of GH therapy on cardiac function in patients with GHD after definitive treatment for acromegaly.

Disclosure: This study was supported by an investigator-initiated grant from Pfizer.

P6

Densely and Sparsely Granulated Somatotroph Adenomas: Are There Any Differences at Presentation?

Niki Karavitaki¹, Olaf Ansorge², Raghav Reddy Gubbihal¹, Simon Cudlip³, John AH Wass¹

¹Oxford Centre for Diabetes, Endocrinology and Metabolism, Department of Endocrinology, Oxford, United Kingdom,

²John Radcliffe Hospital, Neuropathology Department, Oxford, United Kingdom, ³John Radcliffe Hospital, Department of Neurosurgery, Oxford, United Kingdom

Aim: To identify differences at presentation between sparsely and densely granulated somatotroph adenomas.

Patients & Methods: Patients with somatotroph adenoma presenting in our Centre during 2001–2008 were studied. Those offered medical treatment for their acromegaly prior to surgery were excluded. Histological subtype was defined according to the presence of antibody Cam5.2-positive fibrous bodies.

Statistical analyses: Mann–Whitney U and Chi–Square tests.

Results: 30 patients were identified (21 females). 5 had mixed, 8 sparsely and 17 densely granulated tumours. There was no difference in the sex distribution or the age of diagnosis between sparsely and densely granulated adenomas [M:F 2/6 in sparsely and 6/11 in densely – median age 38.5 yrs (range 22–60) in sparsely and 55 yrs (range 25–75) in densely]. There was no difference in the morning fasting GH levels between the 3 types of tumours or between sparsely and densely granulated ones [median 11.3 mcg/L (range 5.4–16.3) in mixed, median 8.7 mcg/L (range 1.5–41.7) in sparsely and median 8.7 mcg/L (range 1.3–283) in densely granulated]. There was no difference in the distribution of micros and macros between sparsely and densely granulated tumours (micros/macros:1/7 in sparsely and 6/11 in densely). Cavernous sinus invasion was more common in the sparsely granulated ones (6/2 in sparsely vs 3/14 in densely granulated; p<0.05).

Conclusions: Apart from cavernous sinus invasion, significant differences at presentation between densely and sparsely granulated somatotroph adenomas have not been found.

Disclosure: Nothing to disclose.

P7

Tibial Nerve Has a Bigger Proportional Enlargement than Median and Ulnar Nerves in Acromegalic Patients: A US Finding

Romana CC Vieira¹, Pedro Madaleno², Fernando Silveira³, Davide MC Carvalho¹

¹Faculdade de Medicina do Porto/Hospital S. Joao, Endocrinology, Porto, Portugal, ²Hospital S. Joao, Radiology, Porto, Portugal,

³Hospital de S. Joao, Neurophysiology, Porto, Portugal

Acromegaly is associated to peripheral neuropathy, either by intrinsic nervous processes (intra and perineural edema) or extrinsic conditions (local compression). The aim of the study was to determine if acromegalic patients (ACRO) have a greater cross-sectional area (CSA) of the median (MN), ulnar (UN) and tibial (TN) nerves and if there is any correlation with neurophysiological parameters. We examined 6 ACRO with active disease – ↑ IGF-1 for age and gender – 5 [female], median age 48 years (range 29 to 58) five with symptoms of peripheral neuropathy in the upper and/or lower limbs and six gender, age and height matched healthy controls. All were submitted to clinical, electrophysiological and ultrasound (US) examination to evaluate the MN, UN and TN, in a total of 24 limbs examined. The nerve CSA of ACRO (MN 8.1 mm²; UN 3.7 mm²; TN 11.9 mm²) was significantly greater ($p < 0.05$) than controls (MN 6.2 mm²; UN 3.0 mm²; TN 5.0 mm²), the tibial one being the most proportionally enlarged compared with controls. The disease duration correlated positively with the right ($Rho = 0.87; p < 0.02$) and left ($Rho = 0.94; p < 0.005$) TN CSA but not with the other nerves CSA. The MN CSA area negatively correlated with the same nerve motor conduction velocity (CV) ($Rho = -0.59; p = 0.04$). The ACRO with symptoms of neuropathy at the hands/feet had higher distal motor latencies (MN 4.2ms; UN 3.0ms; lateral plantar (LP) 5.3ms; medial plantar (MP) 5.1ms) and lower sensitive CV (MN 40.5m/s; UN 54.5m/s; LP 49.0m/s; MP 50.0m/s) than the asymptomatic ACRO (MN 3.7ms; UN 2.8ms; LP 4.1ms; MP 4.2ms and MN 51.0m/s; UN 56.0m/s; LP 56.5m/s; MP 56.5m/s, respectively). We concluded that the CSA of ACRO nerves is significantly greater, the tibial one being the most proportionally enlarged compared with controls. The MN CSA has negative correlation with the same nerve motor VC, suggesting an association of nerve enlargement and nerve dysfunction.

Disclosure: Nothing to disclose

P8

Health-related Quality of Life and Economic Burden in Acromegaly

MC Sheppard¹, S J Pulgar², JM Stephens³

¹Queen Elizabeth Hospital, University of Birmingham, Birmingham, United Kingdom, ²Novartis, Florham Park, New Jersey, United States, ³Pharmerit North America, LLC, Bethesda, Maryland, United States

Background: Treatment goals for acromegaly, an endocrine disorder characterized by elevated levels of growth hormone and insulin-like growth factor-1, have centered around biochemical control. As this becomes more accessible, focus can turn to filling remaining gaps. The objective of this study was to describe the health-related quality of life (HRQoL) burden and the economic impact of acromegaly. **Methods:** A review of the literature from the past 12 years was conducted using QoL, economics, costs and utility as search terms in MEDLINE, Econlit and EMBASE. Additional searches were conducted from article bibliographies and conference proceedings. Selected studies were those designed to examine HRQoL or direct medical costs associated with acromegaly in adults. **Key Findings:** Of 97 abstracts screened, 57 met selection criteria. HRQoL in acromegaly has been assessed using 15 distinct instruments. Patients with acromegaly consistently reported lower QoL than population-based controls. In addition, patients with acromegaly have physical component QoL scores similar to HIV patients, and significantly lower than patients with other diseases such as arthritis and chronic lung disease. Data on the relationship between QoL and biochemical control were equivocal and not consistent across all studies. As for the economic burden, the average direct medical costs per patient varied by study population, geography, and the type/phase of treatment, ranging from \$4,000 to \$28,000 annually. One study showed that costs in the first year after diagnosis were 2–3 fold higher than in other years. Aside from the year following diagnosis, estimated annual costs of care prior to diagnosis were nearly equivalent to annual costs after diagnosis. Costs were generally driven by comorbidities, treatment strategy, and treatment response. Patients who did not achieve biochemical control with treatment had total direct medical costs that were 1.6 times higher than those who were controlled. **Conclusions:** There is a substantial quality of life and economic burden in acromegaly. Treatment and optimization of biochemical control may lead to improvement in QoL and reductions in medical costs. Future areas of research could include identification of dimensions of QoL improved with biochemical control and an evaluation of costs and consequences of varying treatment strategies.

Disclosure: JS is a research consultant for Novartis Pharmaceuticals Corporation.

P9

Impact of Biochemical Control on the Morbidity and Mortality Burden of Acromegaly: A Critical Analysis

Anat Ben-Shlomo¹, Shlomo Melmed¹, Sonia Pulgar², Jennifer Stephens³

¹Cedars Sinai Medical Center, Department of Medicine, Los Angeles, CA, United States, ²Novartis Pharmaceuticals Corp., Florham Park, NJ, United States, ³Pharmerit North America LLC, Bethesda, MD, United States

Background: Controlling GH/IGF-1 levels may reduce the burden of disease. We analyzed whether significant improvement of clinical sequelae are achieved through improved biochemical control. Methods: A 12 year literature review in MEDLINE and EMBASE used acromegaly AND epidemiology, morbidity, mortality, complications, long-term outcomes, and treatment outcomes. Bibliographies and conference proceedings (2003–08) were searched and clinical trials of drug therapies that reported the impact of biochemical control on outcomes were included as were selected studies addressing the relationship between morbidity, biochemical control and long-term outcomes. Results: 109 of 320 publications met selection criteria. Clinical outcome measures shown to improve with GH < 2.5 µg/L and normal IGF-1 included joint thickness (29% reduction), vertebral fractures (2.4 fold reduction), left ventricular function (21% improvement in LVEF, 35% reduction in LVMI), exercise capacity/endurance (30% increase), lipid profile (reductions of 11% LDL, 31% TG, 61% VLDL), and obstructive apnea events (4 fold reduction). Failure to achieve GH/IGF1 control increased mortality risk, especially from cardiovascular and cerebrovascular comorbidities, 1.7–2.3 fold compared with uncontrolled disease. Increased mortality was predicted by less prevalent use of somatostatin analogs, use of radiotherapy, lack of response to therapy and year of data publication. Conclusions: The significant clinical burden of acromegaly encompasses a range of morbidities and reduced life expectancy. The burden of radiotherapy on morbidity and mortality appears significant. Achieving biochemical control through optimal treatment attenuates and even reverses some deleterious consequences of chronic tissue exposure to high GH/IGF-1 levels, including improving life expectancy. Prospective studies are needed to rigorously quantify the relationship between control and long-term outcomes with suboptimal treatment as compared to biochemical remission.

Disclosure: SM and ABS receive preclinical research funding from Novartis.SP is an employee of Novartis. JS is an employee of Pharmerit of North America.

P10

Pasireotide (SOM230) Reduces Pituitary Tumor Volume in Patients with Active Acromegaly: Results From A Phase II Extension Study

Andrew Farrall¹, Matthieu Ruffin², Stephan Petersenn³

¹University of Edinburgh, Edinburgh, Scotland, United Kingdom, ²Novartis Pharma AG, Basel–Stadt, Switzerland, ³University of Essen, Essen, North Rhine–Westphalia, Germany

Introduction: Pasireotide (SOM230) is a multi-receptor ligand somatostatin analogue with high binding affinity for sst1,2,3 and sst5. In a Phase II study of pasireotide in patients with active acromegaly, pituitary tumor volumes decreased significantly by >20% in 39% (20/51) after 1 month octreotide sc followed by 3 months pasireotide. We present preliminary results from the study's extension phase.

Methods: The extension phase enrolled patients who achieved biochemical control (GH ≤2.5 µg/L & normalized IGF-1) or clinically relevant improvement during the core study. Extension-phase patients received pasireotide (200, 400 or 600 µg sc bid) at which clinical benefit was achieved in the core study, with dose adjustments up to 900 µg sc bid if required. Patients continued treatment for as long as benefit was derived. Patients underwent pituitary MRI at core baseline, end of core, then every 6 months until month 28 (extension phase).

Results: 29/30 patients entering the extension study had had core baseline MRI. 9/29 of these patients had achieved significant tumor volume reductions in the core phase and went on to experience further reductions with extended treatment. Of the 20 remaining patients, 4 went on to experience significant tumor volume reduction by 9 months pasireotide treatment, and an additional 3 patients had significant volume reductions by 27 months. Mean percent tumor volume reduction (±SE) was 13% ±3.9% on entry into the extension phase (n=25), 26%±5.9% by 9 months (n=16), and 38%±11% by 27 months (n=5).

Conclusions: While most patients experience tumor volume reductions early in the treatment phase, extended pasireotide treatment significantly reduced pituitary tumor volume in patients with acromegaly. Indeed, patients with significant tumor volume reductions after 3 months benefit further, and extending the treatment resulted in more patients achieving a significant decrease in tumor volume. An additional 7/20 (35%) patients, initially without significant tumor volume reduction, experienced significant tumor volume reductions with extended treatment. Phase III evaluation of pasireotide in patients with acromegaly is currently ongoing.

Disclosure: AF has nothing to disclose; MR is an employee of Novartis; SP is a research consultant for Novartis.

P11

Ectopic Acromegaly Due to Extracranial GHRH-producing Tumors in Japan: Prevalence and Clinical Features

Hideki Katakami¹, S Genka², S Kawa³, S Fujii⁴, T Okajima⁵, E Ishikawa⁶, Y Nishina⁷, H Sugihara⁸, M Kurita⁹, N Hizuka⁹, S Yamada¹⁰, A Matsuno¹¹, S Hashida¹²

¹Teikyo University Chiba Medical Center, Division of Clinical Research Sciences, Department of Medicine, Ichihara, Chiba, Japan, ²Toshima Hospital, Neurosurgery, Tokyo, Japan, ³Shinshu University, 2nd Department of Internal Medicine, Matsumoto, Japan, ⁴Ishikawa Prefectural Central Hospital, Medicine, Kanazawa, Ishikawa, Japan, ⁵National Kyushu Medical Center, Medicine, Fukuoka, Japan, ⁶Miyazaki Prefectural Hospital, Medicine, Miyayaki, Japan, ⁷The University of Tokyo Hospital, Internal Medicine, Tokyo, Japan, ⁸Nippon Medical School, Department of Medicine, Kokyo, Tokyo, Japan, ⁹Tokyo Women's Medical University Hospital, Medicine, Tokyo, Japan, ¹⁰Toranomon Hospital, Hypothalamic and Pituitary Surgery, Tokyo, Japan, ¹¹Teikyo University Chiba Medical Center, Neurosurgery, Ichihara, Chiba, Japan, ¹²Tokushima Bunri University, Human Life Sciences, Tokushima, Japan

Ectopic GHRH-producing tumors can cause acromegaly (eGHRH). However, detailed prevalence, period and levels of hypersecretion of GHRH by tumors have not yet been fully described. The committee of brain tumor registry of Japan, including 281 institutions, disclosed newly 1,604 patients with acromegaly from 1984 to 1996. We developed an ultrasensitive EIA for human GHRH (2fg/tube), surveyed all of suspicious eGHRH, and found three definite cases of eGHRH. The prevalence of eGHRH is, therefore, 0.2% among acromegaly in Japan. Since then, we have experienced additional five patients with eGHRH (n=8), and non-acromegalic patients who showed high plasma GHRH levels (n=3) or slightly higher GHRH levels (n=85). We conclude 1) incidence of eGHRH among acromegaly is 0.2%, 2) a longer period, >10 years, and higher levels of plasma GHRH, >500pg/ml, are necessary to produce clinical features of acromegaly, and 3) measurement of plasma GHRH is the most important diagnostic clue to establish eGHRH.

Disclosure: Nothing to disclose.

P12

Surgical Outcome of GH Producing Pituitary Tumors with Preoperative Use of Octreotide-LAR in Korean Acromegalics

Sung-Woon Kim¹, Sun-Ho Kim²

¹Kyung Hee University School of Medicine, Endocrinology, Seoul, Republic of Korea, ²Yonsei University College of Medicine, Neurosurgery, Seoul, Republic of Korea

Medical therapy of acromegaly has been developed to long acting repeatable (LAR) form of somatostatin analog, Octreotide. The beneficial effects of Octreotide-LAR were potentially suppressed GH, but partially shrunken remnant tumor. The mechanism of tumor shrinkage was documented to apoptosis of tumor cells. The effect of Octreotide-LAR was excellent to control the excessive GH, but final result of effective was under investigation. We checked clinical experience of Octreotide-LAR in Korean acromegalics including characterization of preoperative effectiveness.

We enrolled 30 acromegalics from 2005.4 to 2007.7 at endocrine outpatient clinic of four academic hospitals. Male to female ratio was equal (15/15). Unsuppressed GH confirmed 28 out of 30 patients with oral glucose tolerance test. Average serum GH level was 28.7 ng/mL, and average IGF-I, 985 ng/mL. Micro- to macroadenoma was 8/22 (26%). Before treatment, 28 out of 30 acromegalics were taken 100 mg of somatostatin suppression test, complete responder (GH was suppressed below 1 ng/mL) was 39 % (11/28), lower IGF-I(879±322 vs. 1,035±403 ng/mL) and most of them(6/7, 86%) were microadenoma. Biochemical cure rate after surgery was assessed with suppressed GH after oGTT below 1 n/mL, macroadenoma revealed 67 % (8/12) and 100% (5/5) in microadenoma. Paradoxical response of GH to TRH (18/30) was observed in 78% (14/18) of acromegalics. Overall cure rate with trans-sphenoidal adenoidectomy (TSA) was 80% (16/19). All 3 microadenomas were removed completely.

On focusing to 12 acromegalics, preoperative use of Octreotide-LAR (median duration, 12 weeks) showed complete removal of tumors regardless of tumor size (macro:micro=9:3). Tumor volume, hormone profiles before and after use of Octreotide-LAR showed in

	Before use of LAR	After use of LAR	After Op.
GH, ng/mL ⁴¹	16	1.6	
IGF-I, ng/mL	972	756	396
Tumor size, mm ³	2180	1821	0

But, it clearly depended on surgeon's skill. Preoperative use of Octreotide-LAR should be predicted improvement of surgical outcome, although severe fibrosis was an obstacle to easy removal of tumors after use of Octreotide-LAR.

Disclosure: Nothing to disclose.

P13

Cabergoline as an Adjunctive Treatment in Acromegaly Where Surgery and Somatostatin Analogues Have Failed

Benjamin Jones¹, Violet Sanderson¹, Niki Karavitaki¹, John Wass¹

¹Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, Oxfordshire, United Kingdom

Objective: To investigate the effect on biochemical markers of acromegaly of adding cabergoline in patients who had failed management with surgery and somatostatin analogues.

Methods: Patients with acromegaly who had received cabergoline after failed management with surgery and somatostatin analogues were identified. Growth hormone day curves (GHDC) and serum IGF-I were obtained at 4 time points; post surgery ("baseline"), prior to commencing cabergoline ("TP1"), after 3 months of cabergoline (period during which cabergoline was titrated to the maximum dose) ("TP2"), and the most recent day curve whilst on cabergoline ("TP3").

Biochemical control was defined as mean GH on GHDC ≤ 1.6 mcg/L and serum IGF-I within the reference range.

Comparison of mean GH levels was performed by the Wilcoxon Signed Rank test.

Results: Nine patients were identified. Median duration of treatment was 18 months (range 4 – 72) for somatostatin analogues and 12 months (range 12 – 42) for cabergoline plus somatostatin analogues. Results at the various time points are shown in the **Table**.

	Baseline	TP1	TP2	TP3
Median of mean GH (range)	21.8 mcg/L (4.0 - 49.1)	3.6 mcg/L (1.8 - 44.4)	2.7 mcg/L* (1.0 - 20.1)	2.8 mcg/L* (1.2 - 13.6)
No. patients with mean GH < 1.6 mcg/L (%)	-	-	2 (22.2%)	2 (22.2%)
No. of patients with normal IGF-I (%)	-	2 (22.2%)	3 (33.3%)	2 (22.2%)
No. of patients with biochemical control (%)	-	-	1 (11.1%)	1 (11.1%)
*p<0.05 compared to at TP1				

At both TP2 and TP3, 8 patients (88.9%) had a reduction in mean GH when compared to TP1 (median reduction 32.4% and 41.5%, respectively).

Conclusions: In this small retrospective study we have shown that cabergoline can be an effective adjunctive therapy in subjects with acromegaly which have not responded to treatment with surgery and somatostatin analogues alone; mean GH ≤ 1.6 mcg/L was achieved in 22.2% of patients and significant reduction in mean GH was observed in 88.9% of them.

Disclosure: Nothing to disclose

P14

Recent Epidemiology of Acromegaly in Korea

Obin Kwon¹, Eun Young Park¹, Eun Jig Lee^{1,2}, Young Duk Song², Seong Yeon Kim²

¹Yonsei University Medical College, Internal Medicine, Seoul, Republic of Korea, ²Korean Endocrine Society, Science and Research Committee, Seoul, Republic of Korea

OBJECTIVE: The authors present a retrospective analysis of the epidemiology of acromegaly in recent Korean people.

METHODS: A retrospective review was performed in acromegaly patients who had been treated from 2003 to 2007 at 45 university hospitals in Korea.

RESULTS: Thousand and twenty patients were enrolled. The age ranges (mean) in men and women were 12–79 (41.0) and 9–78 (44.9), respectively. Fifteen percent of the pituitary mass consisted of microadenoma, and the other 85.0% was macroadenoma. The annual incidence and prevalence with age and sex are described in **Table 1**.

Year	n	Incidence per million	Prevalence per million	% male	Mean age at diagnosis (yrs)
2003	116	2.4	9.3	43.8	43.4
2004	134	2.8	12.1	51.7	42.3
2005	118	2.5	14.5	53.8	45.2
2006	153	3.2	17.6	52.4	45.7
2007	136	2.8	20.3	38.2	45.1

Multidisciplinary treatment included transsphenoidal microsurgery and, if necessary, reoperation with/without gamma-knife surgery, radiotherapy and pharmacotherapy. The majority (80.2%) of patients underwent transsphenoidal microsurgery. Radiotherapy and gamma-knife surgery were applied to 7.4% and 9.8% of the patients, respectively. The distribution of prescribed medication is listed in **Table 2**.

Pituitary suppression	Frequency (%)	Hormone replacement	Frequency (%)
Bromocriptine	10.8	Corticosteroid	14.9
Cabergoline	0.9	Thyroid hormone	15.1
Octreotide	31.6	Sex hormone	6.1
Lanreotide	4.1		

CONCLUSION: Compared to previous data, the prevalence and incidence of acromegaly of Korea is low, but the prevalence is increasing annually.

Disclosure: Nothing to disclose.

P15

Pituitary Apoplexy Resulting in Remission of Acromegaly: Summary of Cases

Lisa-Ann Fraser¹, Stan Van Uum¹

¹University of Western Ontario, Department of Medicine, Division of Endocrinology, London, Ontario, Canada

Objective: To identify and present cases of acromegaly who experienced pituitary apoplexy leading to remission of acromegaly with normalization of GH levels.

Methods: Case presentation and review of the literature in PubMed and OVID Medline for reports of similar cases of remission of acromegaly following pituitary apoplexy.

Results: A 43-year-old man presented with classical signs and symptoms of acromegaly and a recent onset of diabetes mellitus. IGF-1 level was 1600 (normal 109–284) µg/L and GH was 93.3 (0.02–1.7) µg/L. There was insufficient GH suppression following OGTT (93.3 to 84 µg/L; normal 0.01–1.7), confirming the diagnosis of acromegaly. A few weeks later, before the initiation of scheduled therapy, the patient presented to a community hospital with pituitary apoplexy. One week later, his IGF-1 had fallen to 179 µg/L and GH to 0.44 µg. After a brief period of mild deficiency in his thyroid and gonadotropin axis hormones, all his pituitary hormones remained normal. His diabetes resolved and he was able to discontinue his diabetes medications. He remained hormonally stable and free of acromegaly during the following year of follow up.

Twenty-one other cases were identified in the literature. Subjective symptoms of apoplexy were present in 20 (91%) of these cases, with headache being the most commonly reported symptom (86%). Other reported symptoms include vomiting (32%), fever (32%), diplopia (32%), ptosis (18%), and visual field defects (5%). Neurologic signs at presentation included nuchal rigidity (18%), change in level of consciousness (23%), photophobia (14%) and seizures (5%). All cases were “cured” of acromegaly, however 68% of cases experienced other pituitary hormone insufficiencies, including four cases who experienced panhypopituitarism.

Conclusions: Pituitary apoplexy can result in cure of acromegaly and in partial or complete pituitary insufficiency. Thus, after (suspected) pituitary apoplexy, pituitary hormone secretion needs to be reevaluated. This may result in starting appropriate substitution therapy and/or changing management of growth hormone overproduction.

Disclosure: Nothing to disclose.

P16

Depression in Acromegalic Patients

Flavia S Jungerman¹, Raquel S Jallad², Felipe HG Duarte², Mara C de Lucia¹, Marcello D Bronstein²

¹ICHC-FMUSP, Psychology Division, Sao Paulo, Brazil, ²HC-FMUSP, Neuroendocrine Unit, Division of Endocrinology and Metabolism, Sao Paulo, Brazil

Background: Acromegaly affects the patient’s physical health and brings great changes in body image, interfering with emotional health. Few studies describe the psychological problems in acromegaly. Generally, the literature limits to address their quality of life, with no in depth attention to depression.

Objective: To assess the presence and severity of symptoms of depression in acromegaly.

Patients: Twenty eight patients (16 females, mean age 46 years (24 to 71 years) were evaluated, four on primary medical treatment (octreotide-LAR=two; octreotide-LAR±cabergoline=two), 12 after transphenoidal surgery only and 16 after radiotherapy (RT) and surgery. IGF-I normalization was observed in 55% of patients.

Methods: Beck Depression Inventory (BDI), validated to Portuguese, was applied. Scores for general population: <17: no depression, from 18–19, depression and >20: severe depression. Results were expressed as mean ±SD, P<0.05 as significant.

Results: 25% of patients presented with depression. The score was 26.1±7.9. Depression was present in 18.2% of men and in 29.4% of women. Men presented a slightly higher score (29.0±9.3) of depression than women (25.0±2.8). The most commonly described symptoms were: fatigue, sleep disturbances, followed by unwillingness to work and irritability. Overall the presence of depression was not correlated to: previous surgery and radiotherapy, hypopituitarism and IGF-I normalization. Nevertheless, presence of previous RT negatively influenced: tiredness and loss of weight and previous RT and surgery negatively influenced symptoms of willingness to work, tiredness and loss of weight. Also, there were differences between those with hormonal deficiency or not in terms of tiredness and loss of weight, and between patients with euthyroidism or hypothyroidism on crying.

Conclusion: Our data demonstrate an increased prevalence of depressive symptoms in acromegaly compared to the general population. As the patient’s hormonal status and treatment conditions did not influence most of the depressive aspects, it seems that physical consequences of acromegaly rather than the disease activity itself contributed for depression. Further studies with larger number of acromegalics are needed in order to support our findings.

Disclosure: MB is a Consultor and Speaker of Novartis Oncology

P17

Successful Pregnancy in Acromegaly with Diabetes Insipidus After Pituitary Tumor Removal: A Case Report

IE Byung Park¹, Sei-Hyun Kim¹, Sihoon Lee¹, Ki Young Lee¹, Yeun Sun Kim¹

¹Gachon University Gil Hospital, Division of Endocrinology and Metabolism, Namdong-gu, Incheon, Republic of Korea

Pregnancy rarely occurs because chronic anovulation usually exists in acromegalics. However, we consider the possibility of pregnancy in child bearing period of woman with acromegaly when H-P-G axis is preserved. Here, we report a case of successful pregnancy and delivery in acromegaly treated with long acting somatostatin analogue (sandostatin LAR), who had diabetes insipidus after transsphenoidal removal of pituitary tumor. A 33-year-old woman visited our hospital because of oligomenorrhea. We diagnosed acromegaly because of typical features, elevated IGF-I (1,095 ng/ml) and paradoxical GH rise in oral GTT. We found pituitary macroadenoma (1.8 cm) on MRI and GH was suppressed on GH suppression test with somatostatin and bromocriptine. We removed pituitary tumor, however, diabetes insipidus was developed. We prescribed desmopressin and bromocriptine. 2 months later after surgery, IGF-I was decreased and combined pituitary function test was normal except FSH response. Residual tumor was detected on MRI (0.8 cm). We increased the dosage of bromocriptine and started sandostatin LAR (20 mg). After 5th sandostatin LAR, IGF-I was normalized. After 7th sandostatin LAR, she became pregnant. Bromocriptine and sandostatin LAR were stopped, however, desmopressin was maintained. She delivered a baby at the 38 weeks of pregnancy without complications.

Disclosure: Nothing to disclose

P18

Surgical Outcome of Transsphenoidal Microsurgery in 200 Growth Hormone Secreting Pituitary Tumors: According to the Shift of Surgical Paradigm

Cheol Ryong Ku¹, Eun Young Park¹, Sun Ho Kim², Eun Jig Lee¹

¹Yonsei University College of Medicine, Department of Internal Medicine, Seodaemun-gu, Seoul, Republic of Korea, ²Yonsei University College of Medicine, Department of Neurosurgery, Seodaemun-gu, Seoul, Republic of Korea

Objective: Transsphenoidal approach (TSA) is a minimal invasive and optimal management for acromegaly when it is caused by growth hormone secreting pituitary tumors. In this study, we evaluated the surgical outcomes of growth hormone secreting tumors according to the shift of surgical paradigm.

Method: Two hundred sixty patients with acromegaly underwent TSA between 1992 and 2007. Among those patients, we evaluated the outcomes of 200 patients who had been followed up with oral glucose tolerance test and cocktail test for pituitary function at least one more time for 1.5 years after surgery. All patients were operated by single neurosurgeon with three different surgical paradigm. Result: Remission occurred in 155 (78%) among 200 patients evaluated. Non-remitted patients compared with remitted ones showed the characteristics of younger age (42.7 ± 11.3 vs. 35.6 ± 9.9 yrs, $P < 0.001$), higher Hardy type ($P < 0.001$), and larger portion of female (32% vs. 10%, $P < 0.001$). Patients with bigger or more invasive tumors tended to aggravate postoperative hypopituitarism ($P < 0.001$), however, there was no difference in the change of postoperative hypopituitarism between total and subtotal adenectomy. In aspects of surgical extent, the more extensive operation showed the higher remission rate (40 vs. 65 vs. 84%; $P < 0.001$) without aggravating the hypopituitarism.

Conclusion: These results indicate that aggressive surgical approach might be critical in the management of acromegaly without increasing the risk of postoperative hypopituitarism.

Disclosure: CK and EP contributed equally to this work.

P19

Assessment of the Awareness and Management of Sleep Apnea Syndrome in Acromegaly in Endocrine Referral Centers in Italy – COM.E.T.A. (COMorbidities Evaluation and Treatment in Acromegaly) Italian Study Group

Ernesto De Menis¹, Andrea Giustina², Annamaria Colao³, Ettore Degli Uberti⁴, Ezio Ghigo⁵, Enio Martino⁶, Francesco Minuto⁷, Paolo Boscani⁸, Gianluca Aimaretti⁹

¹General Hospital, Internal Medicine, Montebelluna, Treviso, Italy, ²University of Brescia, Internal Medicine, Endocrine Section, Montichiari, Brescia, Italy, ³Universita' Federico II, Molecular and Clinical Endocrinology and Oncology, Naples, Italy, ⁴University of Ferrara, Biomedical Sciences and Advanced Therapies, Ferrara, Italy, ⁵University of Torino, Internal Medicine, Torino, Italy, ⁶University of Pisa, Endocrinology and Metabolism, Pisa, Italy, ⁷University of Genova, Endocrinology and Medical Sciences, Genova, Italy, ⁸Ipsen, Milano, Italy, ⁹University of Novara, Clinical and Experimental Medicine, Novara, Italy

In 2007 the Italian COM.E.T.A. study group started to assess the application in a clinical setting of Versailles criteria for management of acromegaly complications. A questionnaire on Sleep Apnea Syndrome (SAS) was delivered by the study group to 107 endocrine centres in Italy. SAS is the first clinical feature suggesting acromegaly in less than 5% of cases. SAS is evaluated in all acromegalic patients in 45.8% of centres and by 53.1% of endocrinologists only in the presence of symptoms. Prevalence of SAS is estimated to be 20–35% and the obstructive type (55.21%) is considered the most frequent form. SAS is perceived as mainly correlated to disease duration and BMI, followed by GH/IGF-I levels, sex and age. SAS is usually confirmed by polysomnography (67%) or by specialist pneumologic consultation (36%). The Epworth Sleepiness Scale is used by 54.3% of the interviewed. Arrhythmias, arterial hypertension and pneumopathias are considered co-morbidities that are improved by SAS treatment. Moreover SAS control is considered very important for patients' quality of life by 67% of specialists. The treatment mostly used to control SAS is Continuous Positive Airways Pressure (CPAP) (79%) even if it is considered poorly accepted by patients (60%). GH/IGF-I normalisation significantly improves SAS according to 80% of the interviewed; 67% consider surgery, medical therapy and radiotherapy as equivalent, although 22% of specialists believe somatostatin analogues (SSAs) to be a better therapeutic approach than the others. Finally 63% of endocrinologists treat SAS in collaboration with other specialists. In conclusion: 1. SAS is a well known comorbidity even if its estimated prevalence is lower than in the literature 2. Polysomnography is the preferred tool for diagnosis 3. Control of SAS is considered relevant both for quality of life and co-morbidities 4. CPAP is the cornerstone of therapy, but patients' acceptance may be critical 5. Control of GH/IGF-I secretion is important to improve SAS 6. Management of SAS requires cooperation between endocrinologists and other specialists.

Disclosure: The study was supported by an unrestricted grant of Ipsen S.P.A.

P20

Malocclusion as a First Sign of Acromegaly: Case Report

Sema Yarman¹

¹Medical Faculty of Istanbul, Internal Medicine, Endocrinology and Metabolism, Istanbul/Çapa, Istanbul, Turkey

Acromegaly is usually recognized because of characteristic manifestations and diagnosed clinically. There is a tendency towards mandibular overgrowth with prognathism, maxillary widening, tooth separation and jaw malocclusion in acromegalic patients. We report a case who is a 18-year-old women with the chief complaint of jaw malocclusion referred to out-patient clinic of internal medicine for investigation of anemia before correction of this abnormality. She had negative upper and lower gastrointestinal (GI) investigations for iron deficiency anemia, and she was based on supplementation due to dietary iron deficiency. Afterwards, she was referred to neuroendocrine consultation for a possible endocrine etiology of malocclusion. Her physical examination was unremarkable for the classic acral or facial changes characteristic of acromegaly. However, she said that her malocclusion had progressed during the last six months. In view of the elevated serum GH (3.48 ng/ml) and IGF1(818 ng/ml ;range 127-424) levels, nonsuppressible GH responses (6.7 ng/ml) in OGTT, and presence of a pituitary adenoma (8x4 mm), the patient was diagnosed as acromegaly. She underwent trans-sphenoidal surgery, and the histopathological diagnosis was GH positive staining adenoma. Despite the absence of the typical manifestations, she reported regression of the soft tissue swelling of her hands, face and feet, postoperatively. In conclusion, acromegaly should be entertained in the differential diagnosis of patients presenting with jaw malocclusion, which poses a diagnostic problem especially in patients who do not have the typical clinical manifestations of acromegaly. So, diagnosis of the early stages of acromegaly is important for preventing the progression to overt acromegaly.

Disclosure: Nothing to disclose.

P21

Glucose Status in Acromegalic Patients Primarily Treated with Somatostatin Analog Lanreotide

Elisabeth Couture¹, Vanina Bongard², Jean-Christophe Maiza¹, Antoine Bennet¹, Philippe Caron¹

¹CHU Larrey, Endocrinology and Metabolic Diseases, Toulouse, Haute Garonne, France, ²CHU Rangueil, Epidemiology, Toulouse, Haute Garonne, France

Objective: To describe changes in glucose status of acromegalic pts during primary lanreotide treatment.

Design: A retrospective, observational single-centre study.

Methods: Glucose status was assessed according to the WHA criteria.

Results: We studied 42 acromegalic pts (18 men, 24 women), median age 50 yrs. At diagnosis, 26 pts had normal glucose status, 8 had impaired glucose tolerance and 8 had diabetes mellitus. Mean dosage of lanreotide was 108 ± 21 mg/month. During lanreotide treatment, median GH decreased (before 12 ng/ml, during 2.1 ng/ml) ($p < 0.01$) and IGF-1 level was age and sex normalized in 33% of pts. Seven pts underwent a deterioration of glucose status whereas 10 pts were improved. Deterioration of glucose status was associated with smaller decrease in GH level (-3.4 versus -10.7 ng/ml, $p = 0.014$). Patients who improved had lower body mass index (25.0 versus 28.7 kg/m², $p = 0.030$) and tended to be younger (47 versus 66 years, $p = 0.051$).

Conclusion: the results of this clinical study attest that primary lanreotide treatment is not associated with significant deterioration of glucose tolerance in acromegalic pts. A small GH decrease is associated with deterioration of glucose status whereas low BMI and young age seem to be predictors of improvement of glucose status in acromegalic pts treated primarily with lanreotide.

Disclosure: PC is a Consultant for Ipsen Biotech

P22

Plasma Apelin Level: A New Marker of Acromegalic Cardiac Disease?

Arzu Gedik¹, Erol Tulumen², Selcuk Dagdelen³, Giray Kabakci², Tomris Erbas³

¹Hacettepe University Medical School, Internal Medicine, Cankaya, Ankara, Turkey, ²Hacettepe University Medical School, Cardiology, Cankaya, Ankara, Turkey, ³Hacettepe University Medical School, Endocrinology and Metabolism, Cankaya, Ankara, Turkey

A specific cardiomyopathy can be detected even in early stages of acromegaly. Apelin is a novel adipokine that increases in early stages of heart failure as a compensatory mechanism due to its peripheral resistance lowering and myocardial contractility increasing effects. Growth hormone has been shown to increase plasma apelin level in a direct fashion.

Objective: To determine whether acromegalic cardiac disease is associated with apelin.

Methods: Twenty eight patients with active acromegaly (AA) (50.1±12.7 yr, 11M/17F, GH: 25.8±10.5 ng/ml, IGF-1: 1042.3±159.6 ng/ml), 27 cured acromegaly (CA) (46.6±8.3 yr, 14M/13F, GH: 1.2±0.4 ng/ml, IGF-1: 407.9±115.3 ng/ml) and 21 healthy control subjects (C) (45.1±7.6 yr, 11M/10F, GH: 0.7±0.1 ng/ml, IGF-1: 304.4±75.0 ng/ml) were included. Plasma apelin levels were measured. Standard and pulsed tissue Doppler Echocardiography parameters were collected. Statistical analyses were performed using SPSS software. The study was approved by the Ethics Committee.

Results: The duration of acromegalic symptoms before the diagnosis in the CA group [median: 7 yr (IQR:1 and 10 yr)] was longer than that of AA group [median: 4 yr (IQR: 2 and 6 yr)] ($p<0.05$). Apelin level was higher in all acromegalics when compared with the controls (1.12 ± 0.5 ng/ml and 0.7 ± 0.4 ng/ml; $p=0.01$). Apelin level in CA group (1.3 ± 0.6 ng/ml) was significantly higher than the level in both AA group (0.9 ± 0.3 ng/ml) and the C group ($p=0.01$, $p<0.01$, respectively). Among the acromegalic patients, apelin level was positively correlated with the duration of acromegalic symptoms before the diagnosis ($r=0.500$, $p<0.01$) and negatively correlated with serum IGF-1 concentration ($r=-0.362$, $p<0.01$). Systolic dysfunction parameters [left ventricle end-diastolic (LVEDD) and end-systolic diameter (LVESD)] were higher in the CA group compared with the C group. LVEDD and LVESD were positively correlated with apelin level in the CA group ($r=0.402$, $p=0.03$; $r=0.414$, $p=0.03$, respectively).

Conclusion: If the diagnosis of acromegaly is delayed too much, the cardiac structural changes cannot be reversed completely later on, even when cure is achieved. Apelin level may be a valuable marker of ongoing cardiovascular risk in cured acromegaly patients with normalized serum IGF-1 level.

Disclosure: Nothing to disclose

P23

Acromegaly Diagnosis and Treatment – Follow Up of 85 Patients in a Single Center

Slawomir A. Mucha¹, Agata Jackowicz¹, Jan Komorowski¹

¹Medical University of Lodz, Clinical Endocrinology, Lodz, Poland

Acromegaly is caused by excessive production of growth hormone (GH) mostly due to a somatotroph pituitary adenoma. The aim of our study is to present our center experience in the diagnosis and treatment of patients suffering from acromegaly.

In this study 85 subjects (49 females, 36 males) hospitalized at the Department of Clinical Endocrinology between 1999–2007 have been evaluated. Most of somatotroph tumors (69 %) were macroadenomas and 31 % were microadenomas at diagnosis. We have also observed one patient with pituitary enlargement and mediastinal tumor with probable ectopic GHRH production. In two cases acromegaly was associated with MEN1 syndrome. Mixed tumors (GH/PRL) have been diagnosed only in 5 subjects (5,9 %). In 3 patients (3,52 %) pituitary apoplexy has been found, but only in one case it was followed by a total pituitary insufficiency.

Treatment outcome could be evaluated in 82 patients. Three patients diagnosed for acromegaly have been recently started with somatostatin analog treatment.

Until now most of our patients (60,97 %) have been operated. From the total number of surgical interventions (56), eleven (19,6 %) were performed transcranially and 45 (80,36 %) were carried out by a transsphenoidal approach. Eleven patients (13,4 %) underwent only surgical treatment, 27 subjects (32,9 %) underwent both surgical and pharmacological treatments. Two patients from our group (2,4 %) have only been irradiated. Seven patients (8,5 %) have been treated both with surgery and radiotherapy and 5 subjects (6,10 %) underwent all available treatment methods. Primary treatment with long-acting somatostatin analogs has been instituted recently in a group of 26 patients (31,7 %). The criteria for cure of the disease have been achieved only in 28 patients (34,1 %).

Due to unsatisfying results of neurosurgery, most of the patients require additional methods of treatment. Better outcome of surgical and pharmacological treatment has been observed in recent years, mostly due to the use of long-acting somatostatin analogs.

Disclosure: Nothing to disclose.

ABSTRACTS
APPETITE/OBESITY

P24

Experiences with Laparoscopic Adjustable Gastric Banding (LAGB) and Sleeve Gastrectomy (SG) in the Treatment of Patients with Childhood Craniopharyngioma and Morbid Obesity

Hermann L Müller¹, Ursel Gebhardt¹, Verena Wessel¹, Sabine Schröder¹, Reinhard Kolb¹, Christoph Wiegand², Niels Sörensen², Jörn Maroske³, Ernst Hanisch⁴

¹Klinikum Oldenburg gGmbH, Dep. of Pediatrics, Oldenburg, Lower Saxony, Germany, ²Evangelisches Krankenhaus, Dep. of Neurosurgery, Oldenburg, Lower Saxony, Germany, ³Verbundklinikum Ansbach, Klinik Rothenburg o.d.T., Dep. of Surgery, Rothenburg, Bavaria, Germany, ⁴Asklepios Klinik, Dep. of General, Visceral and Endocrine Surgery, Langen, Hessen, Germany

Craniopharyngiomas are embryogenic malformations which lead to eating disorders and morbid obesity due to hypothalamic involvement. From 1996 to 2007 we have recruited 401 patients with childhood craniopharyngioma in our trials (HIT-Endo, KRANIOPHARYNGEOM 2000, KRANIOPHARYNGEOM 2007). 40% of all patients with childhood craniopharyngioma developed severe obesity during long-term follow-up. The experience with laparoscopic adjustable gastric banding (LAGB) and sleeve gastrectomy (SG) in obese craniopharyngioma patients is limited.

We are reporting on four patients with childhood craniopharyngioma diagnosed at age 2, 11, 12, and 21 years. BMI-SDS at diagnosis was +0.9, +4.5, +4.7 and -0.1SD. During follow-up, all patients developed morbid obesity (BMI-SDS: +13.9, +10.3, +11.4, +7.3) so that 11, 6, 9 and 3 years after diagnosis LAGB were performed. After a follow-up of 4.5, 1.5, 3.0 and 2.5 years BMI decreased or stabilized continuously in all patients (BMI-SDS at latest visit: +9.9, +9.7, +9.5, +5.9 SD). The eating behavior changed in all patients profoundly. The addiction to food and especially sweets significantly improved based on self-assessment immediately after LAGB. In two patients a dislocation of the LAGB occurred and resulted in weight gain. A 20 years old female received a sleeve gastrectomy (SG) after dislocation of LAGB and experienced short-term weight lost (BMI: 6.57 SD at SG; BMI: 5.00 SD two mo after SG). SG was well tolerated.

We conclude that LAGB could be effective in weight reduction of obese craniopharyngioma patients with hypothalamic syndrome. Close follow-up is necessary in order to analyze long term effects and complications of LAGB and SG in patients with childhood craniopharyngioma and morbid obesity. The question whether immediate LAGB effects on satiety and eating behavior are mediated by the bariatric procedure or by a functional vagotomy due to LAGB has to be further analyzed.

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P25

Chronic β -blocker Therapy is Associated with Lower Physical Activity and Obesity

Paul Lee¹, Jerry R Greenfield¹, Ken KY Ho¹

¹Garvan Institute of Medical Research, Department of Endocrinology, Sydney, NSW, Australia

The sympathetic nervous system is a major regulator of energy balance and substrate utilisation, stimulating energy expenditure and fat oxidation. Pharmacological blockade of the beta-adrenergic system reduces heart rate and physical performance. However it is unclear whether habitual activity is affected. The aims of our study are to determine whether chronic beta-blocker users are more obese and physically less active than non-users. The first part of the study compared Body Mass Index (BMI) waist circumference between beta-blocker users and non-users who attended the Diabetes Clinic (n=219, F=87) and the Hypertension Clinic (n=84, F=17), St Vincent's Hospital, Sydney. The second part of the study compared physical activity of community-dwelling between beta-blocker users and non-users matched for age, gender and BMI using pedometry (steps/week) and structured questionnaires for estimating metabolic equivalents (MET)-hr/day. Amongst outpatients from the diabetes clinic, a cross-sectional comparison revealed BMI to be higher in beta-blocker users (n=64) (33.9 ± 6.3 vs 30.3 ± 6.4 kg/m², p=0.0002) than in non-users (n=150). Amongst outpatients from the hypertension clinic, BMI (32.7 ± 8.6 vs 26.1 ± 4.7 kg/m², p=0.004) and waist circumference (109 ± 16 vs 89 ± 13 cm, p=0.0001) were higher in beta-blocker users (n=42) than non-users (n=42). According to waist circumference criteria used to define the Metabolic Syndrome (>102 cm in men and >88cm in women), 55% of beta-blocker users compared to 21% of non-users were centrally obese (p<0.001). Beta-blocker use was an independent predictor of BMI in multiple regression analyses with age, gender and other medication use in both diabetes and hypertension clinics (adjusted R²=0.21 and 0.32, respectively, p<0.001). Preliminary cross-sectional comparison of community-dwelling chronic beta-blocker users (n=8) with non-users (n=16) showed a significant reduction in pedometry-based physical activity of 38% per week (p=0.03) and a strong trend towards a lower MET-hr/day of 10% (p=0.07). In summary, beta-blocker use is associated with higher BMI and waist circumference, and reduced physical activity. We conclude that beta-blocker use increases obesity, in part due to reduction of physical activity.

Disclosure: Supported by NHMRC Australia

P26

Peripheral Alpha-Melanocyte Stimulating Hormone (α -MSH) in Childhood Obesity and Craniopharyngioma

Hermann L Müller¹, Ursel Gebhardt¹, Thomas Reinehr², Pablo J Enrioni³, Michael A Cowley³, Christian L Roth⁴

¹Klinikum Oldenburg gGmbH, Dep. of Pediatrics, Oldenburg, Lower Saxony, Germany, ²Vestische Children's Hospital, Datteln, Nordrheinwestfalen, Germany, ³Oregon Health and Science University, Oregon National Primate Research Center, Beaverton, OR, United States, ⁴University of Washington, Children's Hospital Research Institute, Seattle, WA, United States

While the majority of energy homeostasis studies focus on central melanocortin action, peripheral effects of melanocortins and their receptors are not well established. Alpha melanocyte stimulating hormone (α -MSH), a posttranslational product of the POMC prohormone and the pituitary pars intermedia lobe melanotrophs, is considered to be the major source of circulating α -MSH in most mammals. Recent evidence shows that α -MSH plays a role in thermal regulation by increasing free fatty acid oxidation (FAO) and glucose uptake in skeletal muscle via activation of MC5R through the PKA-AMPK pathway.

In this study, we aimed to investigate peripheral α -MSH levels in 1) children with simple obesity 2) lean children, 3) children with hypopituitarism, 4) patients with craniopharyngioma (CP) to learn more about the role of peripheral, human α -MSH in obesity and CP. CP patients were recruited in the German craniopharyngioma studies (HIT-Endo, KRANIOPHARYNGEOM 2000/2007). Fasting serum α -MSH was measured by radioimmunoassay with no cross reactivity to ACTH. Furthermore, we measured fasting leptin, insulin and glucose. Interestingly, in patients with hypopituitarism or CP very low to zero α -MSH levels were measured (healthy 26.6 fmol/ml vs hypopituitarism 8.4 fmol/ml vs craniopharyngioma 7.7 fmol/ml). Compared to patients with simple obesity, patients with CP presented with lower ($p < 0.001$) fasting serum α -MSH levels, but there were no significant differences in terms of α -MSH levels between obese and lean children. Low α -MSH levels in CP did not increase one hour after ingestion of a 500 kcal mixed liquid meal. CP patients had higher fasting insulin, insulin resistance index HOMA and leptin levels compared to patients with simple obesity and similar BMI-SDS. The low serum α -MSH levels in patient groups, which have low- or non functioning pituitaries, verify that the pituitary is the critical source for circulating α -MSH. The very low α -MSH levels in CP can be explained by their pituitary or hypothalamic damage and might contribute to severe obesity associated with low thermogenesis.

Disclosure: Nothing to disclose

ABSTRACTS
CELLULAR & MOLECULAR

P27

Reprimo is a Novel Tumor Suppressor Gene in Human Pituitary Tumors

A J Knox¹, M Xu¹, M Edwards¹, K O Lillehei², B Kleinschmidt-DeMasters³, M E Wierman^{1,4}

¹UCD, Med, Aurora, CO, United States, ²UCD, NS, Aurora, CO, United States, ³UCD, Path, Aurora, CO, United States, ⁴Denver VAMC, Res Serv, Denver, CO, United States

Identification of pituitary tumor suppressor genes may provide markers of aggressiveness and lead to a better understanding the pathophysiology of these tumors. Although p53 is not mutated in pituitary tumors, its downstream effectors are candidates for tumor suppressor genes. Reprimo (RPRM) for stop/repress, is a mediator of the p53-induced cell cycle arrest at G2. Prior work suggested that loss of heterozygosity at 2q (RPRM locus-2q23.3) is detected in pituitary tumors. In pancreatic, colon and prostate tumors, RPRM is highly methylated, thus silencing this cell cycle "brake" resulting in increased tumor growth. Comparison of the profiles of ten gonadotropinomas with nine normal pituitaries using Human U133 Plus 2.0 Arrays demonstrated that RPRM was consistently decreased 13-fold in human gonadotrope macroadenomas. RPRM was also decreased 10-fold in a microarray comparison of sparsely versus densely granulated somatotropinomas. RPRM mRNA levels assessed by semi-quantitative PCR were consistently lower in gonadotropinomas and in sparsely granulated, but not densely granulated GH tumors or ACTH tumors compared to normal pituitary. To assess RPRM methylation, the bisulfite converted RPRM promoter (262bp, 30CpG's) was amplified by PCR and sequenced. RPRM promoter methylation, however, was detected in only 3 out of 10 gonadotropinomas, 1 of 3 sparsely granulated, and 0 of 5 densely granulated GH tumors compared to 0 of 10 normal pituitaries. Thus, in contrast to other tumor types, hypermethylation plays only a minor role in suppressing RPRM expression in pituitary tumors. To investigate functional effects of RPRM, RPRM-negative GH3 cells were transfected with vector or flag-tagged RPRM plasmid creating a pituitary cell model of RPRM overexpression. Colony forming capacity was reduced 3.7-fold in RPRM-expressing GH3 cells compared to controls. Further studies showed that, in addition to the downregulation of RPRM and previously reported GADD45γ, both GADD45β and p21 are also repressed in many gonadotrope but not GH tumors. Thus, although p53 itself has not been shown to be dysregulated in human pituitary tumorigenesis, RPRM is one of several downstream effectors of p53 that are inhibited in human pituitary tumors and may play a role in their growth and proliferation.

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P28

Breast Cancer Chemoresistance and GH

Maria Chiara Zatelli¹, Mariella Minoia¹, Carlo Filieri¹, Federico Tagliati¹, Daniela Mole¹, Stefania Leoni¹, Maria Rosaria Ambrosio¹, Ettore degli Uberti¹

¹Section of Endocrinology, University of Ferrara, Dept. of Biomedical Sciences and Advanced Therapies, Ferrara, Italy

Growth hormone (GH) and insulin-like growth factor (IGF-1) promote breast cancer (BC), which mortality is greater in female acromegalic patients as compared to general population. To evaluate whether GH/IGF-1 excess might influence BC response to therapy, we studied the effects of GH and IGF-1 on cell proliferation of a BC cell line, the MCF7 cells, in the presence of doxorubicine (D). GH and IGF-1 induce MCF7 cell growth, protecting them from the cytotoxic effects of D. GH effects are not influenced by an IGF-1 receptor blocking antibody, but are blocked by the GH antagonist Pegvisomant. Resistance to chemotherapeutic drugs may be due to MDR-1, a gene encoding for the P-glycoprotein, which is not induced by GH as assessed by RT-PCR and immunofluorescence. Luciferase activity under the control of c-fos promoter was induced by GH and blocked by Pegvisomant and by D. These data indicate that GH can directly induce resistance to chemotherapeutic drugs with a mechanism that does not involve early gene transcription and support the hypothesis that GH excess might hamper BC treatment, possibly resulting in an increased mortality.

Disclosure: Nothing to disclose

P29

Role of the DRY Motif and the Third Intracellular Loop in Mediating the Intracellular Signaling Elicited by Human Somatostatin Receptor 5

Andrea Lania¹, Erika Peverelli¹, Giovanna Mantovani¹, Paolo Beck-Peccoz¹, Anna Spada¹

¹University of Milan and Fondazione Ospedale Maggiore IRCCS, Endocrine Unit, Dept. of Medical Sciences, Milano, Italy

Somatostatin exerts inhibitory effects on hormone secretion and cell proliferation by interacting with five different receptors (SST1–SST5) linked to multiple cellular effectors, the receptor structural domains involved in these effects being only partially elucidated. Aim of the study was to identify the molecular determinants mediating the interaction of the human SST5 with intracellular signaling in the pituitary cell line GH3, focusing on the BBXXB domain in the i3 loop and the DRY motif in the i2 loop. We analyzed the effects of the SST5 agonist BIM23206 on cAMP accumulation, intracellular calcium, GH secretion, cell proliferation and ERK1/2 phosphorylation in cells expressing either wild-type SST5 or mutant receptors, in particular the naturally occurring mutant R240W in the BBXXB domain and the D136A and R137A mutants in the DRY motif. We found that residues D136 and R137 were critical for SST5 signaling since their substitutions abolished all the intracellular responses. Conversely, i3 loop mutations resulted in receptor that maintained the ability to inhibit intracellular cAMP levels similarly to the wild-type (% inhibition $50 \pm 9\%$ vs $53 \pm 12\%$), but failed to mediate the other responses elicited by wild-type SST5, i.e. reduction of intracellular calcium levels as well as inhibition of ERK1/2 pathway. These events result in an absent inhibition of GH release and an impaired reduction of cell proliferation (% inhibition $38 \pm 7\%$ vs $76 \pm 6\%$ in wt, $p < 0.05$). These data indicate that different regions of SST5 are required for the activation of different signaling pathways.

Disclosure: Nothing to Disclose

P30

Rat Pituitary Expresses a Functional Kisspeptin/Kiss1r System, Regulated by Age, Estradiol and Hypothalamic GHRH and GnRH

Ester Gutiérrez-Pascual¹, José Córdoba-Chacón¹, Leonor Pinilla¹, Raul M. Luque¹, Maria M Malagón¹, Manuel Tena-Sempere¹, Antonio J. Martínez-Fuentes¹, Justo P. Castaño¹

¹Univ. of Córdoba, and CIBER (CB06/03) Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, Dpt. Cell Biology, Physiology and Immunology, Campus Univ. de Rabanales., Córdoba, Spain

It is now widely accepted that kisspeptins and their receptor kiss1r (GPR54) play a key role in the neuroendocrine regulation of the gonadotropic axis by stimulating hypothalamic GnRH secretion. Conversely, despite high kiss1r expression in the pituitary, the role of this system in the gland is still unclear. We recently showed that kisspeptin-10 (kp10) directly acts on rat gonadotropes and somatotropes to stimulate LH and GH release. Here, we analyzed the regulation of this system by physiologically relevant factors, such as postnatal development, hypothalamic GHRH and GnRH, and gonadal steroids (estradiol, E2). Pituitary expression of kiss1/kiss1r dramatically changed from birth to 45 d in an age- and gender-dependent manner. Expression of both kiss1 and kiss1r was the highest in 1-d male pups and decreased thereafter. In contrast, in females, kiss1r mRNA levels also peak perinatally (2d) but kiss1 expression was the highest around puberty (30d). Treatment with GHRH (10^{-8} M, 4h) stimulated kiss1/kiss1r expression in cultured pituitary cells from peripubertal rats, in a gender- and kisspeptin-dependent form, while kp10 (10^{-8} M, 4h) stimulated GHRH-R expression. Conversely, GnRH only increased kiss1r mRNA levels in cultured cells from female rats and kp10 did not influence GnRH-R expression. Long-term (48 h) preexposure of peripubertal rat pituitary cells to E2 doubled the proportion of somatotropes (but not of gonadotropes) responsive to kp10 in terms of free cytosolic Ca^{2+} increase, although these changes did not result in corresponding rises in hormone secretion. Moreover, presence of E2 in the culture medium was critical for the homologous kp10-induced stimulation of kiss1/kiss1r expression, as well as for its heterologous action on GHRH-R expression. Taken together, our results demonstrate that the kiss1/kiss1r system is expressed in the rat pituitary and that its levels are dependent of the age and gender of the animal. Furthermore, kisspeptin exerts a regulatory role on kiss1, kiss1r and GHRH-R expression, which is influenced by gonadal steroids.

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Disclosure: Nothing to disclose.

ABSTRACTS
CRH/ACTH/CUSHING'S

P31

Pure Endoscopic Transsphenoidal Surgery for Cushing's disease: Early Remission and Recurrence. A Single Institution's Techniques, Results, and Outcomes

Davis L Reames¹, Jay Jagannathan¹, Edward R Laws², John Jane Jr.¹

¹University of Virginia, Neurosurgery, Charlottesville, VA, United States, ²Brigham and Women's Hospital, Neurosurgery, Boston, MA, United States

Objective: The efficacy of endoscopic transsphenoidal (ETS) surgery for treating secretory tumors has not been clearly established. This paper examines our four-year experience and details the outcomes for various tumor sizes using a pure ETS approach.

Materials and Methods: A retrospective review from a prospectively acquired database of over 375 patients who underwent pure ETS surgery at our institution from 2004 to 2008. Patients with biochemical (cortisol <3 ug/dL) or clinical signs and symptoms of adrenal insufficiency were started on hydrocortisone. Those that were not in remission by first follow up (1-3 months) were said to have failed surgery. At 12 months patients were classified as in remission or with recurrence. Remission was defined as the continued need for steroid replacement, normal 24-hour urinary free cortisol, or normal serum cortisol.

Results: Forty-six pure endoscopic surgeries for CD were performed on forty-three patients. 13 (28%) represented repeat surgery for recurrence and 2 cases (4%) were debulking procedures. 22 (48%) were microadenomas, 14 (30%) had negative MRI, and 10 (22%) harbored macroadenomas. 28 (61%) surgeries resulted in immediate hypocortisolemia, defined as a serum cortisol level <3µg/dl. 37 (80%) were in remission at first follow up. When all treatment modalities were included, 22 (96%) were in remission at last follow up, while 18 (78%) achieved remission from surgery alone. Microadenomas without prior treatment demonstrated the highest rate of immediate post-operative hypocortisolemia (88%), while initial surgery for MRI negative tumors demonstrated the best rate of remission at 12 months (100%). Mean follow-up was 14 months. Seven patients developed transient DI. Eight patients had post-operative anterior gland dysfunction. No patient experienced a post-operative CSF leak.

Conclusions: ETS is a safe and effective treatment for ACTH secreting pituitary adenomas.

Disclosure: Nothing to disclose

P32

The Performance of Basal and DDAVP Stimulated ACTH Bilateral Simultaneous Inferior Petrosal Sinus Sampling for ACTH Dependent Secreting Tumor Diagnosis

Alessandra Casa Grande¹, P. Tozzatti¹, L. Dornelles¹, D. Mattana¹, Fernando Gastaldo¹, Rollin Guilherme¹, Mauro Antonio Czepielewski¹, Fabiola Costenaro¹

¹PPG Endocrinology, Medicine - UFRGS, Porto Alegre, RS, Brazil

Bilateral simultaneous inferior petrosal sinus sampling (IPSS) for ACTH sample is the most reliable mean for differentiate pituitary (Cushing's disease - CD) and nonpituitary ACTH-dependent Cushing's syndrome (Ectopic Cushing's Syndrome - ECS). Desmopressin (DDAVP) has been suggested as an alternative to CRH. To evaluate the use of DDAVP in IPSS test for ACTH-dependent Cushing's syndrome (CS) diagnosis, it was analysed 36 patients with CS (26 females / 10 males; 29 CD / 7 ECS). All IPSS were performed by the same invasive radiologist, ACTH were measured in inferior petrosal veins and peripheral vein simultaneously, before and 3, 5 and 10 min after IV DDAVP 10 mcg. Threshold for pituitary source were inferior petrosal sinus to peripheral (IPS:P) basal ratio \geq 2:1 or IPS:P ratio \geq 3:1 after DDAVP. Anatomical petrosal vein variability prevented the test in one case with CD. 26 patients with CD had basal ACTH IPS:P > 2.0. Among these CD, 8 failed to obtain DDAVP ACTH IPS:P > 3.0. One patient CD failed to have both gradients and another had just the DDAVP ACTH IPS:P > 3.0. All patients with ECS had IPS:P < 2.0 and < 3.0 at both tests, respectively. Three of them had an identified ECS. In the present study, both tests had the same specificity = 100%. ACTH IPS:P > 2.0 had sensitivity (S) 90% and 77.7% negative predictive value (NPV) for CD and DDAVP ACTH IPS:P > 3 S = 65.5% and NPV = 43.7% had a lower diagnosis accuracy.

Disclosure: Nothing to disclose

P33

Diminished and Irregular Thyrotropin Secretion with Delayed Acrophase in Patients with Cushing's Syndrome

Ferdinand Roelfsema¹, Alberto M Pereira¹, Nienke R Biermasz¹, Daniel M Keenan², Johannes D Veldhuis², Johannes A Romijn¹

¹Leiden University Medical Center, Endocrinology, Leiden, ZH, The Netherlands, ²Mayo Clinic, Endocrine Research Unit, Rochester, MN, United States, ³University of Virginia, Department of Statistics, Charlottesville, VA, United States

Introduction: The suppressive effect of cortisol on serum TSH is well known. Detailed investigations of TSH dynamics in Cushing's syndrome with the newer analytical methods in relation to cortisol secretion are not available.

Patients and Methods: Blood sampling (10 min) for 24 h was performed in 16 patients (PT) with Cushing disease, 11 with adrenal adenoma, 8 after transsphenoidal surgery, 7 treated by unilateral adrenalectomy and pituitary irradiation and 27 controls. TSH secretion characteristics were quantitated by deconvolution, approximate entropy (ApEn) and cosine regression and analyzed by ANOVA and linear regression.

Results: Pulsatile TSH secretion, and mean TSH pulse mass, were diminished during hypercortisolism, independently of etiology ($P < 0.001$). In contrast, TSH secretion was increased in PT in remission due to increased basal (nonpulsatile) secretion ($P < 0.01$). Pulse frequency and half life of TSH were similar in all PT groups. ApEn for TSH was increased in all groups ($P < 0.001$), denoting diminished secretory regularity. Cross-ApEn, a measure of pattern synchrony, was increased in all groups, indicating (partial) loss of secretory synchrony. The TSH rhythm was phase delayed in hypercortisolemic and irradiated PT ($P < 0.01$). Free T₄ levels were decreased in pituitary-dependent hypercortisolism compared with controls ($P = 0.003$). Total 24-h TSH correlated linearly with log-transformed cortisol secretion ($R = 0.52$, $P < 0.001$).

Conclusions: This study demonstrates that cortisol modulates TSH secretion in distinct ways: high cortisol leads to diminished pulsatile release, whereas low cortisol amplifies non-pulsatile release. Diminished TSH secretory regularity in active disease suggests tumoral dysregulation and in remission amplified signaling of TRH or diminished somatostatinergic restraint. These factors may also be responsible for the changed phase setting of the rhythm.

Disclosure: Nothing to disclose.

P34

Good Reliability and Sensitivity to Change of the CushingQoL Questionnaire in Clinical Practice Conditions

Alicia Santos¹, Eugenia Resmini¹, Juan Ybarra¹, Maria-Jose Barahona¹, Maria-Antonia Martinez¹, Camelia Martí¹, Xavier Badia², Susan M Webb¹

¹Hospital Sant Pau, Endocrinology and Centro de Investigación Biomédica en Red en Enfermedades Raras (CIBERER Unit 747); Universitat Autònoma de Barcelona, Barcelona, Spain, ²Health Economics and Outcomes Research, IMS Health, and Centro de Investigación Biomédica en Red en Enfermedades Raras (CIBERER Unit 747), Barcelona, Spain

We described a disease-generated questionnaire to evaluate Health-Related Quality of Life in patients with Cushing's syndrome (CS) (CushingQoL, EJE 2008;158:623-30). Our current aim was to confirm psychometric properties of reliability and sensitivity to change of the CushingQoL questionnaire in clinical practice conditions. Patients and methods: 26 patients (4 men) were evaluated twice, during their routine clinical follow-up. At baseline 13 were hypercortisolemic and 13 not; at follow-up 6 initially active reached endocrine control and 1 initially normal recurred, resulting in 8 being hypercortisolemic and 18 not. Hormonal status (24h urinary free cortisol UFC) and QoL (with the generic EuroQoL-5D and its Visual analogue Score -VAS-, and the CushingQoL questionnaires) were evaluated at baseline and follow-up. Correlations were evaluated with a Pearson's coefficient; data were analyzed with a Student's t test. Results: In 12 patients with controlled hypercortisolism at baseline and follow-up, no change was seen in EQ-VAS (72 ± 19 to 70 ± 15) or CushingQoL scores (62 ± 21 to 58 ± 17). In 9 with hypercortisolism both at baseline and follow-up, no change was observed either (EQ-VAS 58 ± 20 to 57 ± 18 ; CushingQoL 42 ± 16 to 41 ± 24), demonstrating good reliability of the CushingQoL questionnaire in both hypercortisolemic and controlled CS patients. In the 6 initially hypercortisolemic who normalized at follow-up, there was a significant improvement in the CushingQoL score (41 ± 16 to 55 ± 24 , $p = 0.026$) demonstrating good sensitivity to change, with no change in the EQ-VAS (66 ± 15 to 67 ± 16). A negative correlation was observed between UFC and the CushingQoL score ($r = -0.512$, $p = 0.008$). Conclusions: Despite the small study group, the CushingQoL questionnaire (but not EQ-5D-VAS) demonstrates reliability in stable disease (either active or cured), and sensitivity to change after normalization of hypercortisolism; thus, the dimensions included in the CushingQoL questionnaire specifically reflect the problems which determine QoL impairment in CS (Supported by FIS08/0302 and the EU with the ERCUSYN project, PHP200800).

Disclosure: Nothing to disclose

P35

Spinal Epidural Lipomatosis – An Unusual Cause of Paraplegia in Ectopic ACTH Syndrome

Paul Lee¹, Helen Barrett¹, Timothy Steele², Wade Barrett³, Ken KY Ho¹

¹St Vincent's Hospital, Department of Endocrinology, Sydney, NSW, Australia, ²St Vincent's Hospital, Department of Neurosurgery, Sydney, NSW, Australia, ³St Vincent's Hospital, Department of Anatomical Pathology, Sydney, NSW, Australia

Leg weakness in association with Cushing's Syndrome (CS) is usually attributed to cortisol-induced myopathy. Spinal cord compression from cortisol-induced osteoporotic vertebral crushed fractures may cause paraplegia. We present a rare cause of progressive leg weakness and acute paraplegia in a patient with ectopic ACTH syndrome (EAS) from a bronchial carcinoid tumour, secondary to spinal epidural lipomatosis.

A 34 year old man initially presented with hypertension and diabetes to his general practitioner, and clinical suspicion of CS was confirmed by a markedly elevated urinary free cortisol (UFC) excretion of >14000 nmol/day (normal < 300 nmol/day). While awaiting further endocrine evaluation, the patient developed progressive leg weakness, cough and dyspnoea, and was admitted with pneumonia and multiple rib fractures. MRI was performed because of worsening of leg weakness to paraplegia, which demonstrated multiple vertebral crushed fractures without cord compression. However extensive thoracic epidural lipomatosis compressing the spinal cord was evident. Thoracic laminectomy with resection of lipomatosis resulted in improvement of leg strength.

Endocrine investigations revealed a morning plasma cortisol level of 1920 nmol/L and ACTH of 57.2 pg/mL, both of which failed to suppress with an 8 mg dose of dexamethasone (post-dexamethasone cortisol and ACTH levels were 1250 nmol/L and 57.2 pg/mL respectively), indicative of EAS. CT of the chest demonstrated a 2cm nodule in the right upper lobe which revealed avid uptake in a subsequent octreotide/CT scan. A second octreotide-avid focus was found in a right hilar lymph node, suggestive of metastatic disease. Hypercortisolism was controlled with ketoconazole 1800 mg/day which reduced cortisol excretion to 199 nmol/day. A right lobectomy with lymph node clearance was performed. Histology revealed a carcinoid tumour with lymph node metastasis. Postoperatively, UFC excretion was reduced to 11 nmol/24h. The patient made a gradual recovery and regained independent mobility in 6 months, with no biochemical evidence of recurrence.

Spinal epidural lipomatosis is a rare complication of CS and can result in severe neurological sequelae. Radiological screening for epidural lipomatosis may be indicated in patients with CS and lower limb weakness.

Disclosure: Nothing to disclose.

P36

Effectiveness and Safety of Combined Therapy with Low Dose Ketoconazole and Cabergoline in Patients with Cushing's Disease Partially Responsive to Monotherapy with Cabergoline

Rosario Pivonello¹, Monica De Leo¹, Maria Cristina De Martino¹, Alessia Cozzolino¹, Renata S Auriemma¹, Mariano Galdiero¹, Gaetano Lombardi¹, Annamaria Colao¹

¹Federico II University, Department of Molecular and Clinical Endocrinology and Oncology, Naples, Campania, Italy

The first-line treatment of Cushing's disease (CD) is surgery, although it is effective in inducing a long-term remission in around 50% of patients. No pituitary tumor-directed medical treatment is available with the exception of cabergoline, which was demonstrated to control cortisol secretion without major side effects in 40% of patients. Cabergoline has been recently found to induce cardiac valve insufficiency in patients with Parkinson's disease, usually long-term treated with high dose of the drug. A widely used adrenal-directed palliative medical treatment is ketoconazole, which can induce liver damage especially when used at high dose for a long period of time. The aim of the current study was to evaluate the effectiveness and safety of the combined treatment with cabergoline and low-dose ketoconazole in patients with CD partially responsive to cabergoline monotherapy. Six patients with post-surgical persistent CD had been treated with cabergoline at the maximal dose of 3.5 mg/week with a significant reduction but not normalization of urinary cortisol levels (from 530.5136.2 to 258.0107.1 µg/day, $p < 0.05$) associated with a partial clinical improvement after 6 months of treatment. Ketoconazole at the initial dose of 50 mg was added to cabergoline in all patients, and increased by 50 mg every month until normalization of urinary cortisol levels had been achieved. After six months of combined treatment with cabergoline (3.5 mg/week) and ketoconazole (50–200 mg/day), urinary cortisol levels were 107.819.8 µg/day ($p < 0.05$), and were normal in all patients. A significant clinical improvement was observed in parallel with the normalization of cortisol levels. No cardiac valve disease occurred or worsened during the one-year treatment with cabergoline, except for a worsening of tricuspidal regurgitation in one patient. No liver damage was observed in any patient. In conclusion, the combined treatment with cabergoline and low dose ketoconazole is effective and safe in the management of patients with CD who had unsuccessful surgical treatment or are not candidates for alternative definitive treatments.

Disclosure: Nothing to disclose

P37

High Prevalence of Normal Tests Assessing Hypercortisolism in Subjects with Mild and Episodic Cushing's Syndrome Suggests that the Paradigm for Diagnosis and Exclusion of Cushing's Syndrome Requires Multiple Testing

Theodore C. Friedman¹, David E. Ghods¹, Stephen Seasholtz¹, LaTiera Zachery¹, Erik Zuckerbraun¹, Hrayr K. Shahinian², Martin L. Lee¹, Ian E. McCutcheon³

¹Charles Drew University of Medicine and Science, Division of Endocrinology, Metabolism, and Molecular Medicine, Los Angeles, CA, United States, ²Skull Base Institute, Los Angeles, CA, United States, ³MD Anderson Medical Center, Department of Neurosurgery, Houston, TX, United States

Objective: It has been widely accepted that a single determination of eucortisolism or a single demonstration of appropriate suppression to dexamethasone excluded Cushing's syndrome, except in what was previously thought to be the rare patient with periodic Cushing's syndrome. We hypothesize that episodic Cushing's syndrome is relatively common and a single test assessing hypercortisolism may not be enough to accurately rule out or diagnose Cushing's syndrome.

Methods: This retrospective study examined the number of normal and abnormal tests assessing hypercortisolism (24-h urinary free cortisol (UFC), 24-h urinary 17-hydroxycorticosteroids (17OHS), 24-h 17-OHS/g creatinine (17OHS/Cr), 2300 h salivary cortisol and 2300 h plasma cortisol measurements) performed on multiple occasions in 66 consecutive patients with mild and/or episodic Cushing's syndrome compared to a similar group of 54 patients evaluated for Cushing's syndrome, but determined to not have Cushing's syndrome. The Institutional Review Board at Charles Drew University deemed that retrospective review of the collected data was exempt from formal Institutional Review Board review in accordance with federal regulations [45CFR 46.101(b) (4)].

Results: Sixty-five of the 66 patients determined to have Cushing's syndrome had at least one normal test of cortisol status and most patients had several normal tests. The probability of having Cushing's syndrome when one test is negative was 58/64 for 2300 salivary cortisol, 57/66 for 24-h UFC, 53/63 for 24-h 17OHS, 45/61 for 24-h 17OHS/Cr and 31/47 for night-time plasma cortisol.

Conclusions: These results demonstrate that episodic hypercortisolism is prevalent in subjects found to have Cushing's syndrome and no single test is effective in conclusively diagnosing or excluding Cushing's syndrome. Rather, the paradigm for the diagnosis should now be a careful history and physical and in those patients whom Cushing's syndrome is strongly suspected, multiple tests assessing hypercortisolism should be performed on different occasions.

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Disclosure: Nothing to disclose

P38

Radiotherapy May Not Prevent the Development of Nelson's Syndrome

Martha K.P. Huayllas¹, Arthur Cukiert¹, Pedro Paulo Mariani¹, Jose Augusto Burattini¹

¹Clinica Neuroendócrina de São Paulo, Sao Paulo, SP, Brazil

Rationale: Although surgery is generally effective in patients with ACTH-secreting pituitary adenoma, it fails to induce remission in 12% of the patients. Radiation therapy (RT) has long been used as an adjunctive treatment modality in patients with Cushing's disease and was said to reduce the development of Nelson's syndrome in patients not cured by surgery and submitted to bilateral adrenalectomy. We report a patient harboring invasive ACTH-secreting macroadenoma submitted to surgery, RT and adrenalectomy who developed Nelson's Syndrome.

Case Report: A 50 years-old woman presented Cushing's syndrome in 2000. She had insulin-dependent diabetes and hypertension. Plasma ACTH level was 96 pg/ml and urinary cortisol was elevated (510 µg/24hs). Plasma cortisol level was 45 µg/dl (8 AM) and 40 µg/dl after 2mg of dexamethasone. MRI showed macroadenoma (3.5 x 3.3 x 2.0cm) with right cavernous sinus invasion. She underwent transphenoidal surgery and postoperative MRI showed small residual tumor in the right cavernous sinus. She was submitted to stereotactic fractionated radiotherapy in 2000. ACTH plasma level remained elevated (133 pg/ml) and she developed depression and poorly controlled diabetes and hypertension. Bilateral adrenalectomy was performed in 2008; MRI by that time showed tumor occupying the right cavernous sinus (3.0x1.5cm) and ACTH plasma level was 262 pg/ml. Steroid replacement therapy was initiated with prednisone (15mg/day) and fludrocortisone (0.2mg/day). Six months afterwards she developed full cavernous sinus syndrome and skin hyperpigmentation; MRI showed doubling in tumor size. She underwent additional transcranial surgery with partial removal of the tumor. There was no difference between the pathologic findings from both surgical procedures (2000 and 2008).

Discussion: Pituitary irradiation prior to adrenalectomy was found to be protective regarding the development of Nelson's syndrome in patients with persistently active Cushing's disease in some studies. Predictive factors for the development of Nelson's syndrome included high basal ACTH after adrenalectomy, young age and duration of the disease. Radiotherapy was ineffective in our patient in preventing the development of Nelson's syndrome.

Disclosure: Nothing to disclose

P39

Silent Corticotroph Adenoma: Cohort Study of 40 Patients Operated at Emory University

Adriana G Ioachimescu^{1, 2}, Vaninder S Chhabra¹, Matthew J Schniederjan³, Daniel J Brat³, Nelson M Oyesiku¹

¹Emory University, Neurosurgery, Atlanta, GA, United States, ²Emory University, Medicine, Atlanta, GA, United States, ³Emory University, Pathology, Atlanta, GA, United States

Objective: To evaluate the characteristics and outcome of 40 patients with silent corticotroph pituitary adenomas (SCA).

Methods: We reviewed all cases of SCA operated at our center in 1995–2007. Pathology slides were critically reevaluated.

Results: From a total of 1260 surgeries, 40 patients (24 men/16 women, age 49+/-14) were diagnosed with SCA. The characteristics on presentation are shown in **table 1**:

Baseline characteristics	
Characteristics	No. patients (%)
Clinical	
- Headaches	15 (37.5%)
- Visual loss	20 (50%)
- Hypogonadism	13 (32.5%)
- Apoplexy	4 (10%)
MRI	
- Macroadenoma	40 (100%)
- Suprasellar	19 (47.5%)
- Cavernous sinus invasion	17 (42.5%)
Hormonal	
- Hypopituitarism	30 (75%)
- Hyperprolactinemia	15 (37.5%)

No patient exhibited clinical hypercortisolemia. Four patients had previous adenectomy at another center. One patient died on postoperative day 8 due to disseminated intravascular coagulation. Postoperative tumor residue was present in 39% cases, mostly in the cavernous sinus. In 33 patients followed > 6 months (median follow-up 3 years, range 0.5–12.5), recurrence rate was 27%. Permanent endocrine deficiencies affected 75% patients. Six patients had another operation at a median of 15 months later (range 4–84). Twelve patients had radiation therapy at a median of 6 months postsurgery (range: 3–144). Six patients (2 with initial surgery outside Emory) underwent 2 adenectomies and radiation. Of them, 5 had residual tumor on the 3-month postoperative MRI. The predictors of poor outcome in this group were Crooke adenoma in 1 case and MIB index 10% in another. One patient developed elevated ACTH and cortisol postsurgery which normalized after radiation.

Conclusions: We report the largest series of SCA operated by a single neurosurgeon. Residual tumor had an aggressive course in 18% cases, requiring repeated surgery and radiation. Long-term follow-up is warranted, since clinical predictors of re-growth are lacking.

Disclosure: Nothing to disclose.

ABSTRACTS
GROWTH HORMONE

P40

IGF-I AND IGFBP3 IN RELAPSING-REMITTING AND SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

Carolina Di Somma¹, Maria Cristina Savanelli¹, Roberta Lanzillo², Francesca Rota¹, Ermelinda Guerra¹, Paola Contaldi¹, Vincenzo Brescia Morra², Gaetano Lombardi¹, Annamaria Colao¹

¹University Federico II, Department of Molecular and Clinical Endocrinology and Oncology, Naples, Italy, ²University Federico II, Department of Neurological Sciences, Naples, Italy

IGF-1 and IGFBP-3 serum levels are reported to be similar in RR MS and Primary progressive (PP MS) MS patients, although IGFBP-3 was found to relate to progression index in PP-MS. To compare IGF-1 and IGFBP-3 serum levels in relapsing remitting (RR MS) and secondary progressive (SP-MS) courses of Multiple Sclerosis, and to evaluate correlations between serum levels and disease activity and progression. 40 RR-MS and 22 SP-MS patients were enrolled. Patients were followed up for two years with clinical, MRI and laboratory investigations. IGF-1 and IGFBP-3 were measured by radioimmunoassay kits at baseline (before interferon therapy was started) and at follow-up. A secondary progression index was calculated for SP patients. Serum levels of IGF-1 and IGFBP-3 were not different in the two MS patients groups at all timepoints. No significant correlations were found between serum levels and pre-treatment clinical and MRI (enhancement) data, although patients with high IGFBP-3 levels showed a tendency to have a higher number of enhancing lesions at baseline ($p=0.066$). Secondary progression index did not relate to IGFBP-3. 30 patients were followed-up for 2 years (26 with MRI). Differences of enhancement between baseline and follow-up did not relate to changes in serum levels of IGF-1 and IGFBP-3. In conclusion, serum levels of IGF-1 and IGFBP-3 are not different in RR and SP patients and are not related to pre-treatment clinical and neuroradiological markers of disease activity and to changes of MRI activity during therapy. Secondary progression index is not related to IGFBP-3, in contrast to what has been described for PP MS patients. IGFBP-3 levels tend to be higher in patients with more active disease at MRI.

Disclosure: Nothing to disclose

P41

Evidence for Central Regulation by Estrogen of GH Secretion in Women: A Study of the Effects of Estrogen Receptor Antagonism

Vita Birzniece¹, Akira Sata¹, Selina Sutton¹, Jennifer L Evans¹, Ken K Y Ho¹

¹Pituitary Research Unit, Garvan Institute of Medical Research and Department of Endocrinology, St. Vincent's Hospital, Darlinghurst, NSW, Australia

In men, stimulation of GH secretion by testosterone requires prior aromatisation to estrogens, an effect unmasked by estrogen receptor blockade with tamoxifen. The role of estrogen in the central regulation of GH secretion in women is poorly established. Estrogen supplementation by a physiological non-oral route fails to stimulate GH secretion in postmenopausal women. While this observation has questioned the role of circulating estrogen, it does not exclude an effect of estrogens produced locally from aromatisation. To investigate further a putative role of estrogen on the GH system, we studied the effects of tamoxifen in ten healthy postmenopausal women on the peak GH response to arginine, and on IGF-1 and SHBG levels. Measurements were obtained before and after treatment with 10 and 20 mg/d tamoxifen for two weeks each in an open-label sequential study. Data were analysed by paired t-tests and significance determined after Bonferroni's correction. When compared to baseline, peak GH concentration was reduced significantly by the 20 mg dose (13.6 ± 4.4 vs 4.2 ± 1.4 mIU/L; $p < 0.05$) but not the 10 mg dose of tamoxifen (9.4 ± 2.8 mIU/L). Mean IGF-1 concentration was also reduced significantly by the higher (16 ± 1.6 vs 12.3 ± 1.6 nM/L; $p < 0.01$) but not the lower dose of tamoxifen (14.5 ± 1.6 nM/L). Mean SHBG levels increased significantly ($p < 0.01$) in a dose dependent manner from 48.3 ± 7.9 to 60 ± 9.4 and 61.9 ± 9.9 nM/L, respectively. In summary, in postmenopausal women, tamoxifen reduced peak GH response to arginine and decreased IGF-1 but increased SHBG levels. The increase in SHBG is consistent with a known hepatic estrogen agonistic effect which is likely to inhibit IGF-1 production from the liver. The finding of a blunted peak GH response to stimulation despite reduced IGF-1 feedback inhibition indicates profound central suppression of GH output by tamoxifen. This study demonstrates that estrogens regulate central GH secretion in women. The contrasting effects on GH status between estrogen supplementation and receptor blockade suggest a paracrine mechanism and an important role of aromatase in the neuroregulation of the GH system.

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Disclosure: Nothing to disclose

P42

Neuroendocrine Regulation of Growth Hormone and Androgen Status by Selective Estrogen Receptor Modulators in Healthy Men

Vita Birzniece¹, Akira Sata¹, Jennifer L Evans¹, Ken K Y Ho¹

¹Pituitary Research Unit, Garvan Institute of Medical Research and Department of Endocrinology, St. Vincent's Hospital, Darlinghurst, NSW, Australia

In men, the stimulation of GH and inhibition of LH secretion by testosterone (T) requires aromatisation to estradiol. Drugs which block central estrogen action, such as Selective Estrogen Receptor Modulators (SERMs), may affect pituitary function. The aim was to investigate whether therapeutic doses of commonly used SERMs (tamoxifen, raloxifene) perturb GH and androgen status in normal men. Ten healthy men (mean age 64.8±3 years) were randomised to 2-week sequential treatment with tamoxifen (Tam; 10 and 20 mg/d) and raloxifene (Ral; 60 and 120 mg/d) with washout of 2 weeks in between. Peak GH response to arginine stimulation test, serum IGF-I, LH, T, and SHBG levels were measured before and after each treatment period. Data were analysed by paired t-tests with significance determined after Bonferroni's correction. Neither tamoxifen nor raloxifene significantly changed peak GH response. Tamoxifen but not raloxifene reduced IGF-I levels. Both drugs significantly increased LH and testosterone concentrations. Tamoxifen but not raloxifene significantly increased SHBG levels. The maximal reduction in IGF-I and increase in testosterone concentrations was greater with tamoxifen than with raloxifene treatment.

	Baseline	Tam 10mg	Tam 20mg	Ral 60mg	Ral 120mg
GH (mIU/L)	13.8±5.2	13.6±5.9	9.1±2.9	7.4±2.6	9.8±2.5
IGF-I (nM/L)	18.9±1.6	18.5±2.1	14±1.6	*20±1.9	17.4±1.9
LH (IU/L)	3±0.2	4.4±0.6*	5.4±0.7*#	4.7±0.5*	3.7±0.5
T (nM/L)	14.8±1	18.6±1.7	22.6±2*#	18.6±1.5*	18±1.5*
SHBG (nM/L)	33.5±3.4	40.9±4.1*	38.9±3.5*	36.4±3.4	34.4±3.1

* p<0.05 vs baseline; # p<0.05 vs Ral 120mg

In summary, tamoxifen but not raloxifene suppress GH status. Both tamoxifen and raloxifene increased androgen status with tamoxifen imparting a greater effect.

In conclusion, therapeutic doses of tamoxifen perturb central regulation of the GH and gonadal axes to a greater degree than raloxifene. The SHBG response suggests tamoxifen but not raloxifene exert hepatic estrogen agonistic effect. Tamoxifen and raloxifene exert different central and peripheral effects on the GH and gonadal axes.

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Disclosure: Nothing to disclose

P43

Pituitary Functions in Young Ischemic Stroke Patients: Preliminary Data

Carolina Di Somma¹, Maria C Savanelli¹, Antonella Tufano², Francesca Rota¹, Dario M N Di Minno², Gaetano Lombardi¹, Giovanni Di Minno², Annamaria Colao¹

¹University Federico II, Department of Molecular and Clinical Endocrinology and Oncology, Naples, Italy, ²University Federico II, Department of Clinical and Experimental Medicine, Naples, Italy

Both animal and human studies suggest that the GH-IGF axis is involved in the pathogenesis of ischemic stroke. The aim of this study was to assess the presence of endocrine alterations in young patients experiencing ischemic stroke. At this purpose, in 24 patients affected with stroke, pituitary function was tested 6–12 months after the ischemic event. In all patients (12 Males, 12 Females; aged 18–45 yrs; BMI: 26.8±3.5 kg/m²), basal endocrine parameters and the GH response to GHRH + arginine test (using BMI-dependent cut offs) were evaluated. Hypopituitarism was found in 10 (41.6%) of the 24 patients. The most common pituitary deficits were, in decreasing order: GH deficit in 6 (25%), LH/FSH deficit in 2 (8.3%) and hypocortisolism in 2 (8.3%). While deficit of TSH and diabetes insipidus was not recorded in any patients. In addition, IGF-I levels were less than 2 SD in 6 patients (25%). Concordance between impaired GH response after GHRH+ARG and low IGF-I levels was found in 3 (50%) out of 6 patients. In conclusion, hypopituitarism was found in young patients 6–12 months after ischemic stroke. Thus, endocrine evaluation and neuroendocrine follow-up of patients experiencing ischemic stroke should be performed on a regular basis, in order to monitoring pituitary function and eventually providing appropriate replacement. Whether this finding can influence the clinical outcome of primary disease remain to be clarified.

Disclosure: Nothing to disclose

P44

Waist is Superior to BMI and Waist-to-Height Ratio for the Prediction of Peak GH in Healthy Individuals

Marianne Klose¹, Ulla Feldt-Rasmussen¹

¹Copenhagen University Hospital, Rigshospitalet, Dept of Endocrinology, Copenhagen, Denmark

Body: Background & aim: Growth hormone (GH) secretion is heavily influenced by BMI, and BMI related cut-offs have been advocated. We tested the hypothesis that measures of central fat distribution rather than BMI determine stimulated GH secretion in healthy adults, with special attention to the possible superior role of the waist-to-height ratio (WHtR).

Subjects and Methods: Thirty healthy subjects (15 men) with a median BMI of 24 kg/m² (19 – 30) underwent a GHRH+arginin test and an ITT, one week to one month apart. Body composition was assessed by: BMI, waist (W), waist-to-hip (WHR), WHtR and total and abdominal fat mass assessed by dual energy X-ray absorptiometry (DXA). Local Ethical Committee approval was obtained.

Results: Peak GH in response to the GHRHarg test was negatively correlated to BMI ($r=-0.50$; $p=0.005$), WHtR ($r=-0.55$; $p=0.005$), W and WHR (both $r=-0.66$; $p<0.001$), whereas not to total ($r=-0.20$; $p=0.3$) or abdominal ($r=-0.30$; $p=0.1$) fat mass. Multiple regression analysis demonstrated a combined influence of BMI ($\beta=0.33$) and gender ($\beta=0.33$); $\text{adjR}^2=0.31$. Replacement of BMI with W eliminated the independent role of gender ($\beta_{\text{waist}}=-0.60$); $\text{adjR}^2=0.41$.

Peak GH in response to the ITT was negatively correlated to total ($r=-0.39$; $p=0.05$) and abdominal ($r=-0.35$; $p=0.07$) fat mass, whereas not to W ($r=-0.03$; $p=0.9$), WHtR ($r=-0.02$; $p=0.9$) or any of the other body composition measures ($p>0.4$).

Conclusion: Our data suggests that waist, as the simplest measure of central adiposity, is more appropriate than BMI for future stratification and establishment of GH cut-off points especially as concern the argGHRH test. Waist is moreover suggested as superior to WHR, WHtR, total and regional fat mass as assessed by DXA

Disclosure: This presentation was made possible by an unrestricted grant from Novo Nordisk.

ABSTRACTS
GROWTH HORMONE DEFICIENCY

P45

Prediction of the Response to Growth Hormone (GH) Therapy in Growth Hormone Deficient (GHD) Adults

Edna Barbosa¹, Josef Koranyi¹, Helena Filipsson¹, Bengt-Åke Bengtsson¹, Cesar Boguszewski², Gudmundur Johannsson¹

¹Sahlgrenska University Hospital, Department of Endocrinology, Gothenburg, Sweden, ²Hospital de Clinicas da Universidade Federal do Paraná, SEMPR, Serviço de Endocrinologia e Metabologia, Paraná, Brazil

Objective and design: We developed a prediction model for serum IGF-I, body fat (BF) and lean body mass (LBM) using logistic regression analysis. 167 patients (103 men), with GHD (median age 50 years) were studied during 12 mo of GH therapy. GH dose was individually titrated to obtain normal serum IGF-I. Good responders (GR) and poor responders (PR) were defined as patients above or below the median in the changes in IGF-I, BF and LBM. Body composition was measured by DXA. **Results:** The best predictors for IGF-I were gender and basal insulin levels. Males were 6.7 times more likely to be GR in IGF-I compare to females ($p < 0.0001$). Patients with higher insulin were more likely to be GR in IGF-I (OR: 1.06, $p = 0.05$). The IGF-I model correctly predicted 70% of the GR or PR. For BF response, patients with higher BMI are less likely to be GR in BF (OR: 0.82, $p = 0.002$). Patients with higher BW were more likely to be GR in BF (OR: 1.05, $p = 0.01$). The model correctly predicted 65.9 % of the GR or PR. For LBM, patients with higher BMI are less likely to be GR in LBM (OR: 0.71, $p < 0.0001$) and patients with higher BF were more likely to be GR in LBM (OR: 1.09, $p = 0.01$). LBM model correctly predicted 67% of the GR or PR. **Conclusion:** Our models have a good ability to predict the response to GH, however, they do not explain all variability in the responses.

Disclosure: EB and JK have nothing to disclose; HF received lecture fees from Nycomed, Novo Nordisk and Pfizer; CB consults for Merck Serono; BB has equity interests in Tercica and received lecture fees from Pfizer; GJ consults for Merck Serono, Duo Cort AB and received lecture fees from Pfizer and Novo Nordisk.

P46

Analyses of Treatment Variables for Patients with Childhood Craniopharyngioma – Results of the Multicenter Prospective Trial KRANIOPHARYNGEOM 2000 After Three Years of Follow-up

Hermann L Müller¹, Ursel Gebhardt¹, Rolf-Dieter Kortmann², Andreas Faldum³, Torsten Pietsch⁵, Monika Warmuth-Metz⁴, Reinhard Kolb¹, Christoph Wiegand⁷, Gabriele Calaminus⁶, Niels Sörensen⁷

¹Klinikum Oldenburg gGmbH, Pediatrics, Oldenburg, Lower Saxony, Germany, ²University Hospital, Radiooncology, Leipzig, Saxony, Germany, ³University, IMBEI, Mainz, Rheinlandpfalz, Germany, ⁴University Hospital, Neuroradiology, Würzburg, Bavaria, Germany, ⁵University Hospital, Neuropathology, Bonn, Nordrheinwestfalen, Germany, ⁶University Hospital, Pediatric Oncology, Munster, Nordrheinwestfalen, Germany, ⁷Evangelisches Krankenhaus, Neurosurgery, Oldenburg, Lower Saxony, Germany

Controversies surround various treatment variables for patients with childhood craniopharyngioma such as growth hormone (GH) replacement, which some believe can exacerbate recurrence/progression. In the multicenter prospective trial KRANIOPHARYNGEOM 2000 (www.kinderkrebsinfo.de/kranio2007) we analyzed the impact of risk factors on the incidence and time course of relapses after complete resection and tumor progressions after incomplete resection in patients with childhood craniopharyngioma. Multivariate analyses of risk factors (age at diagnosis, degree of resection, irradiation, GH-treatment and gender) and descriptive analyses of overall (OS) and event-free survival (EFS) rates were performed in 117 patients from Germany, Austria and Switzerland, recruited prospectively during 2001 and 2006 and evaluated after 3 years of follow-up. We observed a 3-year-OS of 0.97 and a 3-year-EFS of 0.46, indicating high recurrence rates after complete resection (CR) ($n = 47$; 3-year-EFS: 0.64) and high progression rates after incomplete resection (IR) ($n = 64$; 3-year-EFS: 0.31). The risk of an event decreased by 80% after CR compared to IR (hazard-ratio=0.20; $p < 0.001$). Irradiation had protective effects on EFS: irradiated patients had an 88% lower risk of recurrence/progression compared to patients without / before irradiation (hazard-ratio=0.12, $p < 0.001$). GH treatment had no impact on 3-year-EFS rates. There was a trend (p -value of the score-test: $p = 0.065$) towards lower EFS in patients diagnosed with craniopharyngioma at young age. Tumor recurrences / progressions are frequent and occur early after initial treatment of childhood craniopharyngioma. A radical resection preserving the integrity of hypothalamic structures appears optimal at original diagnosis. Irradiation was efficient in preventing recurrences / progressions. GH treatment had no impact on high recurrence/progression rates observed during short-term follow-up.

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P47

Vitamin D Elevates Growth Factor

Steven Woodworth², Zoe Woodworth¹

¹CLK High School, Calumet, MI, United States, ²Aspirus Keweenaw, Laurium, MI, United States

Observations in clinical practice suggested that Vitamin D supplementation affects Insulin-like Growth Factor-1 (IGF-1) serum levels. A retrospective search of billing records identified 88 patients with more than one serum IGF-1 measurement since 2006, whose records were reviewed for simultaneous 25-OH Vitamin D serum measurements. Serum assays had been done at the Warde Medical Laboratory in Ann Arbor Michigan. Patients on growth hormone or changing uses of thyroid, DHEA, paroxetine, escitalopram, or oral estrogen were excluded because of known or suspected effects on IGF-1, leaving 26 paired samples, with less than a year between sampling. Women predominated (20/26), and average patient age was 51 years (age range 28–81 years). Average serum IGF-1 before Vitamin D supplementation was 91.5 ng/ml (range 42–156 ng/ml)(standard deviation 27.3). Initial serum 25-OH Vitamin D averaged 24ng/ml (58nmol/l)(range 6–57 ng/ml)(standard deviation 12). Elevation of IGF-1 after Vitamin D supplementation occurred in 25/26 pairs ($p < .05$ by sign test and paired t-test). The average increase of IGF-1 was 25.7% (range -5% to +92%). The average increase in 25-OH Vitamin D after supplementation was 84% (range 0%–230%), after an average of 3.4 months (range 1–11 months). Supplementation varied in type, strength, and source; with eleven using 50,000 iu Vitamin D2 per week, and the rest using Vitamin D3 at doses of 1,200–10,000 iu/day. Three patients had no rise in serum 25-OH Vitamin D after supplementation, yet had increases of IGF-1 (average 17% rise). Six of the patients had initial 25-OH Vitamin D levels (range 31–57ng/ml) above the accepted normal cut-off of 30ng/ml, and all of those had increases of IGF-1 after Vitamin D supplementation (average 26% gain). The highest initial Vitamin D level (57ng/ml) increased to 76ng/ml after 2 months, with IGF-1 increasing by 40%. Conclusion: Vitamin D supplementation manifests significant increases in serum IGF-1, even when initial serum 25-OH Vitamin D levels are above the accepted normal cut-off of 30ng/ml.

Disclosure: Nothing to disclose

ABSTRACTS
MISCELLANEOUS

P48

Empty Sella and Anterior Hypopituitarism in a Patient Affected by Hemochromatosis Type 3 with Biallelic TFR2 Mutations

Eugenia Sacco¹, Bianca M Ricca², Silvia Majore³, Francesca Lugli¹, Annalisa D'Uonno¹, Marilda Mormando¹, Serena Piacentini¹, Antonio Bianchi¹, Alfredo Pontecorvi¹, Laura De Marinis¹

¹Catholic University, Endocrinology, Rome, Italy, ²Catholic University, Hematology, Rome, Italy, ³University of Rome La Sapienza, Medical Genetics, Rome, Italy

Introduction: Hemochromatosis (HHC) is a cause of hypopituitarism, characterized by increased iron absorption and iron release from reticuloendothelial system. The iron accumulation causes multiorgan failure resulting in several clinical features. About 80% of the HHC patients present mutations in HFE gene (classic HHC) but mutations have been found in other genes as HJV, HAMP, TFR2 (HHC type 3) and SLC40A1. Non-HFE related HHC differs from classic form.

Case report: We present a case of an Italian 51-year-old man. When 31 years old, he presented fatigue, erectile dysfunction, headaches, arthralgia and insulin dependent diabetes mellitus. Then, atrial paroxysmal fibrillation appeared requiring ablation of the accessory conduction pathway. The patient came to our observation at the age of 47. We found biochemical evidence of iron overload and HHC was diagnosed. Pituitary function evaluation was performed with evidence of anterior hypopituitarism and diencephalic magnetic resonance imaging showed an empty sella. The patient started appropriate hormonal replacement therapy and phlebotomy regimen. Genomic DNA was extracted and reverse hybridization assay showed the p.E60X heterozygous mutation in TFR2. Sequencing of TFR2 entire coding regions and splice sites identified a second mutation, p.R105X.

Conclusion: In patients affected by HHC, mutations in TFR2 gene are reported in 21 cases only, 14 of whom of Italian origin. The mutation, p.R105X, was previously characterized in only two affected siblings from a France family. As the hemochromatosis is a cause of hypopituitarism, the iron study should be performed in all patient with "idiopathic" hypopituitarism and not just in hypopituitary patients with normal pituitary imaging. HHC type 3 occurs at a younger age with severe clinical manifestations and significant iron overload started years before the onset of symptoms. In HHC type 3, extra-pituitary features, including hypopituitarism can appear relatively early and can be reversible if promptly recognized and treated.

Disclosure: Nothing to disclose

P49

Foreign Body Granuloma Associated to Rathke's Cyst – Case Report

Valter A S Cescato¹, Sergio Rosemberg², Lara V Machado¹, Malebranche B C Cunha Neto¹, Nina R C Musolino¹

¹Hospital das Clinicas, University of S. Paulo, Medical School, Functional Neurosurgery Division, S. Paulo, Brazil, ²Hospital das Clinicas, University of S. Paulo, Medical School, Pathology Department, S. Paulo, Brazil

The majority of the solid-cystic sellar masses are apoplectic pituitary adenomas or craniopharyngiomas. Inflammatory lesions of the pituitary gland are rare. We present a patient with hypopituitarism, diabetes insipidus whose MRI suggested pituitary apoplexy but the surgery diagnosed a Rathke's cyst and the pathological diagnosed a foreign body granuloma. Case report: 54 years old female patient complained about amenorrhea, polyuria and polydipsia since 5 years ago. The hormonal evaluation disclosed multiple pituitary deficiencies: secondary hypothyroidism (free T4=0.51 ng/dL, TSH=0.03mU/mL), low gonadotropin levels (LH<0.07IU/L, FSH=1.31IU/L), adrenal insufficiency with low ACTH levels (cortisol=2.0 ug/dL, ACTH=9pg/mL), and slight hyperprolactinemia (PRL=84ng/mL). Mean diuresis of 5 liters/day. She started hormonal replacement with prednisone, levothyroxine and desmopressin. MRI revealed a 22x20x19mm sellar mass with a suprasellar extension, slightly compressing the optic chiasm. The lesion was heterogeneous, isointense in the sellar portion and hyperintense in the suprasellar portion on T1-weighted images, and slightly high signal on T2-weighted images. After gadolinium only the intrasellar lesion and the boundaries of the suprasellar portion enhanced. The patient was operated on by the transsphenoidal approach for a presumed apoplectic pituitary macroadenoma. After the dural opening a fibrous firm lesion was found and submitted to resection. Subsequently, it was drained a fluid compatible with Rathke's cyst. Microscopically, the pathological conclusion was foreign body granulomatous hypophysitis. The literature reported rare cases of the granuloma associated to Rathke's cyst. Hypopituitarism is frequent in these cases, and diabetes insipidus is more common than in pituitary adenoma. Our patient complained short history of amenorrhea and polyuria. Diabetes insipidus is rarely associated to the initial picture of pituitary adenoma. We hypothesize that the foreign body granulomatous process occurred due to leakage of cyst contents, with destruction of pituitary tissue.

Disclosure: Nothing to disclose

P50

Cholestasis Secondary to Hypopituitarism in an Infant with Septo-optic Dysplasia and Syndactilia

Gayla Karaguzel¹, Emel Gül Okur¹, Ahmet Sari², Aysenur Ökten¹

¹Karadeniz Technical University, School of Medicine, Pediatric Endocrinology, Trabzon, Turkey, ²Karadeniz Technical University, School of Medicine, Radiology, Trabzon, Turkey

Septo-optic dysplasia (SOD) consists of the association of congenital midline brain abnormalities and optic nerve hypoplasia combined with pituitary hormone deficiency. One third of patients with SOD has the complete triad. To date, cholestasis and digital anomalies has been reported only in a few SOD cases. We present a nine-week-old male was referred to our hospital for evaluation of prolonged jaundice. On physical examination, his weight 6.7kg (97. percentile), height 63cm (97.percentile), jaundice, optic disc hypoplasia, hepatomegaly, syndactilia of 1st - 3rd digits on the left hand. Laboratory data on admission revealed elevated direct bilirubin, alanine aminotransferase, lactate dehydrogenase. Electrolytes, glucose and urine organic acids profile were normal. An abdominal ultrasound demonstrated hepatomegaly. Liver biopsy showed giant cell transformation of the liver cell. Throughout his hospitalization, the patient was noted convulsion associated with hypoglycemia. At the time of hypoglycemia, his cortisol and growth hormone levels below normal, free thyroxine 0.68ng/dL, thyrotropin 4.25uIU/mL, insulin and c-peptide levels was below detectable assay limits. Hypopituitarism was considered, and MRI demonstrated pituitary hypoplasia, absence of pituitary infundibulum, optic nerve atrophy, ectopic neurohypophysis. Hydrocortisone and thyroxine therapies were started. His blood glucose levels stabilized and cholestasis resolved within 2 months after initiation of therapy. He is now eleven months old with well growth and euglycemic state, but he had ocular problems. Mutations within HESX1 are a rare cause of SOD and hypopituitarism. Further molecular studies will certainly help us in understanding the pathogenesis of SOD and associated abnormalities. Congenital hypopituitarism is an uncommon cause of neonatal cholestasis, but the clinician must be alert an infant presenting with cholestasis and hypoglycemia to the possibility of hypopituitarism.

Disclosure: Nothing to disclose.

P51

Harvey Cushing's Radical Attempt at Human Pituitary Transplantation

Courtney Pendleton¹, Hasan Zaidi¹, Gustavo Pradilla¹, Aaron Cohen-Gadol², Alfredo Quinones-Hinojosa¹

¹Johns Hopkins School of Medicine, Department of Neurosurgery and Oncology, Baltimore, MD, United States, ²Indiana University, Department of Neurosurgery, Indianapolis, IN, United States

Harvey Cushing's innovations in the treatment of pituitary disorders have been well documented in the literature. However, the details of his early career at the Johns Hopkins Hospital, where his interest in the pituitary gland began, have remained largely unknown. A review of the archived records from 1896–1912 revealed new information about Dr. Cushing's radical changes to the practice of medicine. In 1911, Dr. Cushing performed the first documented pituitary gland transplant, using tissue obtained from a stillborn fetus to treat a patient with hypopituitarism, who required daily injections of whole-gland extract. Following the operation, the patient discontinued his daily injections, and remained symptom free for six weeks. The patient later required a second transplant, which used tissue from a stillborn full-term infant. This review demonstrated that, contrary to contemporary speculation that the patient died from the transplant, he succumbed to pneumonia a month after the second transplant. Dr. Cushing's use of fetal tissue to repair an endocrine defect, though radical for his time, is supported by ongoing research into the role of pituitary stem cells in regenerating functional tissue in vivo.

Disclosure: Nothing to disclose.

P52

Management of Acquired Partial Central Diabetes Insipidus in Pregnancy

Sonia Ananthkrishnan¹

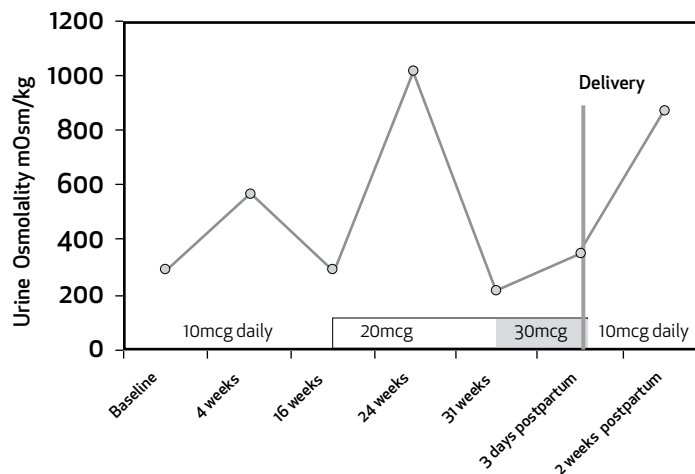
¹Boston University School of Medicine/Boston Medical Center, Section of Endocrinology, Diabetes and Nutrition, Boston, MA, United States

Objective: To review a case of acquired partial central diabetes insipidus (DI) in pregnancy, and discuss the causes, pathophysiology and management of this condition. This case highlights the need for increased dosing of dDAVP during pregnancy in women with this condition, due to placental vasopressinase-mediated clearance of residual endogenous pituitary arginine vasopressin (AVP).

Case presentation: A 32 year old female presented for management of her partial central DI in pregnancy. She had been managed on low-dose intranasal dDAVP prior to pregnancy and required progressive increases in dose during pregnancy to control her polyuria. She safely delivered a healthy child following a spontaneous vaginal delivery at term, and her dDAVP dose was reduced to baseline postpartum.

Results: Serial serum sodium concentration, serum osmolality and urine osmolality were followed throughout the pregnancy at frequent intervals and guided the dosing of intranasal dDAVP.

Figure 1: Urine Osmolality During Gestation with dDAVP Dose



This patient required a 200% increase in dDAVP dose during pregnancy. Following pregnancy, AVP-NP11 gene analysis is being performed to further evaluate the exact etiology of her central DI.

Discussion: Worsening polyuria in this pregnant patient necessitated increased dosing of dDAVP due to accelerated clearance of residual pituitary AVP. Unlike dDAVP, endogenous AVP is degraded by placental vasopressinase during pregnancy. Although there is a lack of prospective randomized controlled trials, dDAVP has been used safely in managing DI in pregnancy.

Conclusion: A 32 year old woman with acquired partial central DI carried a healthy pregnancy to term. She required close monitoring of her urine and serum osmolality and a progressive 200% increase in dDAVP dose during the course of her pregnancy.

Disclosure: Nothing to disclose

ABSTRACTS
PROLACTIN

P53

Outcome of Dopamine Agonists in Men with Macroprolactinomas

Sema Yarman¹, Neslihan Kurtulmus²

¹Istanbul Faculty of Medicine, Istanbul University, Department of Internal Medicine, Division of Endocrinology and Metabolism, Istanbul Tıp Fakültesi, Capa, Istanbul, Turkey, ²Vakıf Gureba Educational Hospital, Endocrinology, Vatan Caddesi, Fatih, Istanbul, Turkey

The long-term therapeutic responses of dopamine agonist drugs (DAs; bromocriptine and cabergoline) therapy in men with macroprolactinomas have been partially studied. Therefore, we identified a retrospective chart review for evaluate the clinical presentation, medical management, and treatment outcomes of male with macroprolactinomas. We obtained 22 male patients with macroprolactinomas, mean age of 47yr (range, 20–67yr) at diagnosis, who were treated with DAs alone. Baseline clinical characteristics are described by the patients as a history of impotence (77%), decreased libido (73%), headache (64%), visual abnormalities (41%), gynecomastia (9%), and galactorrhea (4.5%). The mean pretreatment serum PRL level was 2067 ng/ml (range, 196–10382). Before therapy, the mean maximal tumor diameter was 29mm (range, 14–55). Thirteen patients had visual field defect, 16 had hypogonadism, 4 had hypothyroidism, and 8 had hypocortisolism. All patients were followed for a mean of 57 months (range, 5–142). After initiating of DAs, serum PRL was returned to normal in all (100%). The patients noted marked improvement in sexual function and headache within 2–3 months of therapy. Complete resolution of visual field defect observed in eleven. During the evaluation of the pituitary function at follow-up, a subset of patients required thyroid (n:5), testosterone (n:6), and glucocorticoid (n:3) replacement therapy. Based on serial radiological studies, in most patients tumor shrinkage continues progressively with time, and the mean tumor shrinkage was 62% (range; 20–100%), it was disappeared in 3, and partial empty sella developed in two. Three patients have not been taking DAs therapy since 4 yr. In conclusion, we found that normalization of serum PRL occurs in 100% of men with macroprolactinomas, even do giant adenomas, and a remarkable shrinkage was observed in all macroadenomas. DAs were also decreased the incidence of pituitary deficiency syndromes. Therefore, DAs are still the first-line drug for treatment of all macroprolactinomas.

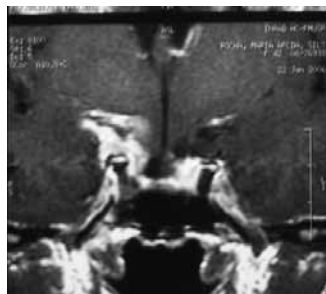
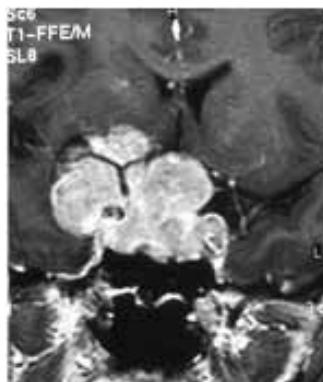
Disclosure: Nothing to disclose

P54

Secondary Resistance to Dopamine Agonists During the Long Term Treatment of a Macroprolactinoma

Nina R C Musolino¹, Malebranche B C Cunha Neto¹, Gilberto Ochman Silva¹, Valter A S Cescato¹

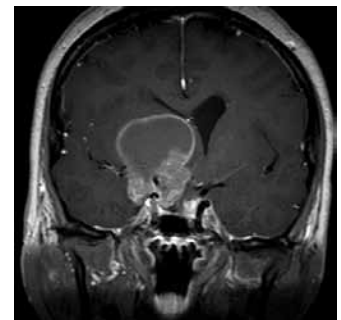
¹Hospital das Clinicas, University of S. Paulo, Medical School, Functional Neurosurgery Division, S. Paulo, SP, Brazil



Resistance to dopamine agonists (DA) occurs in about 15% of prolactinomas but in some cases the control of the tumor growing is obtained even with no prolactin (PRL) normalization. In these cases the long-term medical therapy can progressively reduce the PRL levels. We present a 44 y old female patient. She have a prolactinoma diagnosed 9 years ago due to amenorrhea, visual loss and epilepsy. At that time the MRI showed an invasive tumor. She was initially treated with bromocriptine (up to 35mg/d) with clear tumour shrinkage and PRL reduction (from 1490 to 190 ng/mL). After 7 years of therapy the PRL levels increase (1240ng/mL)

despite the use of high doses of cabergoline (7mg/week) and the MRI showed solid/cystic tumor expansion.

The first approach was a cyst puncture when 23mL of fluid was drained and the PRL in this material was > 26,000ng/mL. Tumor recurrence occurred after few weeks and the patient underwent surgical debulking by pterional route. The literature reports rare cases with secondary resistance to DA, the increase on the PRL levels can be a cue to this event.



Disclosure: nothing to disclose

P55

Discrimination of Prolactinoma from Hyperprolactinemic Nonfunctioning Tumor

Jae Won Hong¹, Sun Ho Kim^{2,3,4}, Eun Jig Lee^{1,2,3}

¹Endocrinology, Yonsei University College of Medicine, Seoul, Republic of Korea, ²Institute of Endocrinology, Yonsei University College of Medicine, Seoul, Republic of Korea, ³Pituitary Tumor Clinic, Yonsei University College of Medicine, Seoul, Republic of Korea, ⁴Neurosurgery, Yonsei University College of Medicine, Seoul, Republic of Korea

It is often difficult to discriminate prolactinoma from hyperprolactinemic nonfunctioning tumors in clinical field. Nonfunctioning pituitary tumor or dopamine resistance is suspected when patients with hyperprolactinemic tumors are not responding to dopamine agonist therapy. It is important to determine the timing of surgery because long term use of dopamine agonist (DA) may cause fibrosis around tumor and adverse effect during operation and postoperative period. We retrospectively evaluated the treatment outcome of the patients with hyperprolactinemic pituitary tumor and analyzed the discriminating characteristics in order to build an appropriate therapeutic strategy for hyperprolactinemic pituitary tumors.

We included 155 patients with hyperprolactinemic pituitary tumors from 2005 to 2008 at Yonsei University College of Medicine, Seoul, Korea. Patients were divided into 3 groups according to the treatment outcome: (A) prolactinoma responding to DA treatment, (B) Prolactinoma requiring surgical treatment and (C) hyperprolactinemic nonfunctioning tumor. Last two groups were diagnosed by immunohistochemical staining of resected tumor tissues.

Seventy-four patients showed decreased serum prolactin levels and tumor size with administration of DA. Surgical treatment was required in 81 patients. Postoperative pathological analysis was available in 34 cases, and immunohistochemistry revealed that 26 were positive for prolactin and 8 were negative. Patients with hyperprolactinemic nonfunctioning pituitary tumors at initial visit have older in age (44.0±13.2, 34.1±12.9, 34.9±11.2, respectively) and lower in median serum prolactin levels (51.1, 172.9, 106.2, respectively) than those of the patients with prolactinoma responding to DA treatment and prolactin positive prolactinoma requiring surgical treatment. When prolactin level was less than 100 ng/mL, the positive rate for prolactinoma by immunohistochemical study was 65% (13/20). However, the positive rate increased up to 83% (5/6) in the level of prolactin was from 100 to 200 ng/mL. In prolactin level was more than 200 ng/mL, the positive rate was 100% (8/8). In conclusion, patients with prolactinoma tend to be younger and higher serum prolactin levels at initial visit.

Disclosure: Nothing to disclose.

P56

Functional Role of the Her2/Neu receptor in Stably Transfected Rat Prolactinoma Cells

Hidenori Fukuoka¹, Song-Guang Ren¹, George Vlotides¹, Shlomo Melmed¹

¹Cedars-Sinai Medical Center, Department of Medicine, Los Angeles, CA, United States

Objective: We recently reported pathways underlying regulation of pituitary tumor gene expression by epidermal growth factor (EGF), heregulin and pituitary ErbB receptor ligand signaling. Therefore, we now tested the role of Her2/Neu, an ErbB receptor family member, in hormone regulation and cell proliferation in prolactinoma cell lines as a possible target for drug therapy.

Methods: We generated both constitutively active (Her2CA) as well as kinase deficient (Her2KD) Her2/Neu stable GH3 cell transfectants, and tested PRL and GH gene expression by Real Time PCR, and hormone secretion by RIA. Cell proliferation was detected by WST-1 assay and confirmed by colony formation. Intracellular cell cycle signaling was examined by western blot. Statistical analysis accounted for multiple groups.

Results: After selection and propagation of stable GH3 cell transfectants, PRL gene expression (mRNA levels) was markedly enhanced (~ 60-fold) in constitutively active Her2/Neu stable transfectants (Her2CA-GH3) compared with empty vector transfectants (Figure 1). PRL secretion was induced 6-fold in Her2CA-GH3 cells ($p < 0.01$). Her2CA-GH3 cells showed significant increases in cell proliferation (1.8 fold, $p < 0.01$) from day 5 of incubation. In contrast, transfectants expressing the kinase deficient form of Her2/Neu (Her2KD-GH3) did not exhibit enhanced cell proliferation compared to controls. Her2CA-GH3 cells also showed significantly higher colony formation in soft agar than controls (31 ± 1.6 vs 12 ± 1.3 colonies per field, $p < 0.01$). The percentage of Her2CA-GH3 cells in S phase increased from 23 ± 0.3 to 29 ± 0.3 %. By western blotting, phosphor-Rb protein levels were shown to be induced (~ 1.3-fold) in Her2CA-GH3 cells, further confirming the increased number of cells in S phase.

Conclusions: Her2/Neu induces PRL secretion and regulates GH3 cell proliferation by increasing S phase of the cell cycle and enhancing phosphor-Rb levels. This receptor could therefore be an effective target for medical therapy of dopamine receptor agonist resistant prolactinomas.

Disclosure: Nothing to disclose

ABSTRACTS
TUMORS

P57

Macroprolactinomas (MAC) in Men Are More Aggressive Than in Women: Study of Clinical Features, Outcome of Patients and Ki-67 in Tumor Tissue

Patricia Fainstein Day¹, Mariela Glereani¹, Soledad Lovazzano¹, Andrea KozaK¹, Marta Balzaretto¹, Silvia Christiansen¹, Antonio Carrizo¹

¹Hospital Italiano, Endocrinology, Buenos Aires, Argentina

We have previously communicated that MAC in men are bigger and prolactin levels higher than in women. Other authors have related this finding to a delay in diagnosis. Our hypothesis is that MAC in men are more aggressive independently of possible delay in diagnosis. A retrospective study of 71 MAC (42 men) was carried out. The parameters studied were age, signs and symptoms at presentation, onset of symptoms, basal prolactin, estradiol (E2), total testosterone (To) levels, tumor size and Ki 67 expression in tumor tissue of patients referred to surgical treatment.

RESULTS: Male patients were older. The time elapsed from the onset of symptoms to diagnosis was shorter in men although not significantly. Visual defects were significantly more prevalent in men. Hardy 4 stage tumors were found only in men. We found no significant correlation between tumor size and the age of the patients nor between tumor size and the onset of symptoms. Whereas basal E2 levels (21.2 ± 12.9 vs 33.3 ± 43.3 pg/mL, $p=ns$) were very similar in male and female patients, To levels were significantly higher in men (0.6 ± 0.5 vs 1.4 ± 1.2 ng/mL, $p=0.02$). Among the eighteen patients referred to surgical treatment (11 men), only men ($n=8$) presented acute neurologic symptoms. The rate of cell proliferation represented by Ki 67 was significantly higher in tumors in men (3.5 ± 1.2 vs $1.5 \pm 0.5\%$, $p=0.0001$). No significant correlation was found between Ki 67 expression and tumor size.

This is the first study focused in MAC that shows that they are clinically and biologically more aggressive in men. Thirty percent of male patients had normal To levels. Hypogonadism in men could appear later in the progression of prolactinomas and this might explain that they were older at the time of diagnosis. Furthermore, To could be a source for E2 "in situ" biosynthesis giving male tumors an advantage in cell proliferation.

Disclosure: Nothing to disclose

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Crooke's Adenoma: University of Florida Experience

Greg Murad¹, Steven Roper¹, Anthony Yachnis¹, Karen Brezner¹, Laurence Kennedy^{1,2}

¹University of Florida, Gainesville, Florida, United States, ²Cleveland Clinic, Cleveland, Ohio, United States

Excess levels of circulating cortisol are associated with the development of Crooke's hyaline change – accumulation of perinuclear cytokeratin filaments – in pituitary corticotrophs. In classical Cushing's disease the corticotrophs in the non-adenomatous part of the pituitary are affected while the adenoma cells typically are not. In 1981 Felix et al (Acta Neurochir 58:235-43) described 3 women with Cushing's disease in whom many tumor cells showed Crooke's change. Fewer than 50 cases of "Crooke's adenomas" have been reported. We report on 6 Crooke's cell adenomas identified from 479 pituitary tumor cases operated on by a dedicated pituitary neurosurgeon (SNR) at the University of Florida since 2000. Patients' ages ranged from 34 to 61 years at time of initial surgery; 5M/1F. Only one patient, a 39 year old man, presented with Cushing's syndrome; pituitary MRI was negative but inferior petrosal sinus sampling confirmed the pituitary as the source of ACTH; a pituitary microadenoma was removed and postoperative cortisol was 4.1 mcg/dL at 48h. Symptoms and signs of Cushing's syndrome, with biochemical confirmation of hypercortisolism despite a second pituitary operation at which more adenoma tissue was identified and removed, persisted. One patient with a macroadenoma presented with pituitary apoplexy; two other patients had hypogonadotropic hypogonadism, another had hypothyroidism (assumed central, but already on levothyroxine when referred), and the final macroadenoma was an incidental finding on MRI. One patient had visual loss. During a mean follow up of 29 months three patients had recurrence of tumor (including the Cushing's patient), one of whom has required 4 additional operations and radiation therapy. Postoperative endocrine outcomes were: persistent Cushing's syndrome in one, hypogonadism in two, hypothyroidism in two, growth hormone deficiency in two. Our experience is consistent with the impression that Crooke's adenomas tend to be more aggressive and recurrent than other pituitary adenomas, but are much less likely than typical corticotroph adenomas to cause Cushing's syndrome.

Disclosure: Nothing to disclose

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A Novel Classification for Pituitary Adenomas of the Null Cell Type

Hideki Katakami¹, Shozo Yamada²

¹Teikyo University Chiba Medical Center, Div Clin Res Sci, Dep Medicine, Anesaki, Ichihara, Chiba, Japan, ²Toranomon Hospital, Hypothalamic and Pituitary Surgery, Tokyo, Japan

Null cell adenoma (NC), composing 10–15% of all pituitary adenomas, have no hormone immunoreactivity and no other immunohistochemical markers of specific adeno-hypophysial cell differentiation, though some of them show electron-dense secretory granules in their cytoplasm. In an attempt to elucidate hypothalamic functions by measuring hypothalamic hormones in both cavernous sinus/peritumorous blood (Ce) and peripheral blood (Pe) during transsphenoidal surgery, we found high SRIF levels in Ce, but not Pe, of a female patient with a pituitary adenoma of the null cell type. In the present study, we characterized SRIF gene expression and production in a large series of patients with pituitary adenoma. We simultaneously measured SRIF levels by a highly sensitive RIA in both Ce and Pe of 179 patients with immunohistologically verified pituitary adenomas (male/female:80/99, age:13–75, GHomas 79, gonadotropinomas (NF) 54, ACTHomas 22, PRLomas 4, TSHomas 2, arachnoid cyst 1 and NC 17). We also measured quantitatively SRIF contents and mRNA levels in fresh–frozen tumor samples. We then characterized qualitatively SRIF production by a specific SRIF immunohistochemistry and HPLC. In 10 out of 17 patients with NC, we found high SRIF levels in Ce (19.4–589.4pg/ml), but not Pe (3.3–7.2pg/ml). SRIF levels in other types of adenomas were not significantly elevated in both Ce and Pe (2.0–8.0pg/ml). When we measured both SRIF contents and gene expression in tumor samples by the RIA and a real time PCR, respectively, NC with high SRIF levels, SRIF1–28 dominant, in Ce showed significantly higher tissue SRIF contents and gene expression than those of NC without high SRIF levels or other types of pituitary tumors. SRIF-IHC showed a dense staining in tumorous tissues of NC with high Ce SRIF levels, but not other types of pituitary tumors. SRIF–negative NC showed higher FSH–beta gene expression than SRIF–positive NC. These results suggest that NC is classified further by SRIF–production.

Disclosure: Nothing to disclose

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In–vivo Assay of Folate Receptors of Non–functioning Pituitary Adenomas with Tc99m–Folate SPECT/CT

James R. Galt¹, Raghuvier K. Halkar¹, Naema A. Osman², Timothy H. Fox³, Bajat A. Faraj¹, Chheng–Orn Evans², Kush Kumar¹, Houping Wang², Nelson M. Oyesiku²

¹Emory University, Department of Radiology, Atlanta, GA, United States, ²Emory University, Department of Neurosurgery, Atlanta, GA, United States, ³Emory University, Department of Radiation Oncology, Atlanta, GA, United States

Objectives: Evaluation of in–vivo assay of folate receptors in non–functional pituitary adenomas using pre–operative Tc–99m folate (Folatescan, Tc–99m EC20, Endocyte, Inc.) SPECT/CT compared with Western blot analysis (WBA) of surgical specimens. **Methods:** A prospective analysis of 51 patients (M:F=27:24, age:29–82 years of age) with clinically non–functional pituitary adenomas on MRI underwent pre–operative imaging using 25 mCi Tc–99m folate. Patients were treated with cold (non radioactive) folate (0.5–1.0mg IV) prior to tracer injection. SPECT/CT, whole body and lateral head planar images were acquired approximately 2 hours post–injection. Surgical resection took place within a week. WBA on a section of the excised specimen assessed folate–receptor expression. Attenuation corrected Tc–99m folate SPECT/CT images were assessed qualitatively and quantitatively (maximal tumor counts/background) with WBA as gold standard.

Results: Integrated CT proved valuable for uptake localization and region of interest (ROI) placement. Qualitative SPECT/CT yielded sensitivity of 96% and specificity of 55%. Receiver operating characteristics (ROC) analysis of quantitative uptake yielded a tumor/background cutoff ratio of 3.5 with sensitivity of 83% and specificity of 80%. Scalp uptake yielded consistent results (over brain, neck, and choroid plexus) for background when SPECT/CT misalignment artifacts were avoided. Detection of pituitary uptake was hampered in anterior–posterior and lateral images by facial uptake, which varied between patients.

Conclusions: SPECT/CT of Tc–99m folate is an accurate method of assaying folate receptors in–vivo and could serve as a quantitative marker for identifying folate receptor positive adenomas for selection of patients for folate–targeted therapy of clinically non–functional pituitary adenomas for which there is currently no medical therapy.

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Silent Corticotroph Adenomas Have Unique Recurrence Characteristics Compared with Other Non-functioning Adenomas

Eun K Lee¹, Hwa Y Cho¹, Hong I Kim¹, Ji W Yoon¹, Hwa Y Ahn¹, Jee H An¹, Seong Y Kim¹

¹Seoul National University College of Medicine, Department of Internal Medicine, Seoul, Republic of Korea

Objective The prevalence of silent corticotroph adenomas (SCAs) is not rare among non-functioning pituitary adenomas (NFPAs). However, whether the clinical significance of SCAs differs from that of NFPAs without ACTH immunoreactivity (non-SCAs) has been on debate. We aimed to compare the natural history and other clinical characteristics of SCA with non-SCA control group.

Design/patients We reviewed medical records of all patients who underwent transsphenoidal surgery for NFPAs from January 1990 to October 2007 at the Seoul National University Hospital.

Measurements We analyzed whether age, sex, clinical manifestations at diagnosis such as symptoms, hormonal alteration, preoperative tumor size and invasiveness, postoperative recurrence rate and characteristics of recurrence differed significantly between SCAs and non-SCAs.

Results Twenty eight patients with SCAs and 134 patients with non-SCAs were analyzed. Mean age at the time of diagnosis was 44 (range, 13–67) years in SCAs and 50 (18–79) years in non-SCAs ($P=0.026$), with follow-up period of 5.3 (range, 1.0–16.0) and 4.2 (0.5–16.1) years ($P=0.184$). Overall recurrence rates of SCAs and non-SCA were 25.0% and 26.9% ($P=.839$). Multiple recurrences of more than 2 times ($P=0.001$), and recurrence after more than 5 years ($P=0.040$) were associated with SCAs. In SCAs, patients with recurrence were diagnosed at younger age than patients without recurrence.

Conclusion The overall recurrence rates of SCAs and non-SCAs were similar. However, patients with SCAs had unique recurrence characteristics and more aggressive behavior when they recur compared with non-SCAs. Therefore, we suggest that patients with SCAs need more careful long-term monitoring, especially when they were diagnosed in young age.

Disclosure: Nothing to disclose

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Neurocognitive Effects of Conventional Radiotherapy in Patients with Pituitary Adenomas

Beatriz Lecumberri¹, Javier Estrada², José García-Uría³, Luis Caballero⁴, Ana Ruiz⁴, Felipe Pallardo¹, Tomás Lucas²

¹La Paz Hospital, Endocrinology, Madrid, Spain, ²Puerta de Hierro Hospital, Endocrinology, Majadahonda, Madrid, Spain,

³Puerta de Hierro Hospital, Neurosurgery, Majadahonda, Madrid, Spain, ⁴Puerta de Hierro Hospital, Psychiatry, Majadahonda, Madrid, Spain

Neurocognitive effects of cranial radiotherapy have been widely described in children, but there is still no consensus about their presence and features in adults. Recent studies suggest that radiotherapy produces a potentially reversible impairment on hippocampal adult neurogenesis. Our aim was to assess the effects of conventional radiotherapy (R) on cognitive functions of adult patients treated for pituitary adenomas (P) and explore the factors that could modulate them. We randomly selected 124 patients with P, 45 men and 79 women, aged 50.3 ± 12.8 years, 66 with acromegaly (A), 33 Cushing's disease (C), 8 prolactinomas, 15 nonfunctioning, 1 TSHoma and 1 gonadotropinoma, treated with transsphenoidal surgery (S), 56 of whom received postoperative R, and recorded their main clinical data, and the results of a neuropsychological evaluation using Mini-Mental, Benton, Wisconsin (W) and Barcelona (B) Tests. A cerebral SPECT was performed in 8 patients. No differences in sex, age, average duration of symptoms before diagnosis, type of P, treatments for disease control and prevalence of cured patients were found between S only and R groups. However, R group showed larger tumors at diagnosis, higher rates of pituitary deficits at the time of the study and significantly lower age-adjusted scores on B Story Recall Test ($p<0.0001$) and W ($p<0.0001$) when compared to S group. All the SPECTs from R patients (5) revealed the same pattern of hypoperfusion on temporal lobes involving cortical areas. In multivariate analysis R was the only factor associated with worse results in both tests. The probability of getting lower scores with time was related to R total dose ($p<0.05$) and field size ($p<0.01$) and significantly higher for acromegalic patients irradiated after 40 years of age than before ($p<0.005$) the same as in patients with C than those with A ($p<0.02$). In our study postoperative R produced a clear impairment on verbal memory and executive function of adult patients with P. Kaplan-Meier survival curves suggested that age at R and type of P modulate the development of radiation-induced cognitive decline.

Disclosure: Nothing to disclose

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Low O⁶-Methylguanine-DNA Methyltransferase (MGMT) Expression and Response to Temozolomide in Aggressive Pituitary Tumors

Ann McCormack¹, Kerrie McDonald¹, Anthony Gill², Morton Burt³, Miguel Debono⁴, Richard Ross⁴, Ashley Grossman⁵, Bruce Robinson⁶, Roderick Clifton-Bligh¹

¹Kolling Institute of Medical Research, Sydney, NSW, Australia, ²Royal North Shore Hospital, Sydney, NSW, Australia, ³Flinders University, Adelaide, SA, Australia, ⁴University of Sheffield, Sheffield, United Kingdom, ⁵Barts and the London School of Medicine, London, United Kingdom, ⁶University of Sydney, Sydney, NSW, Australia

Background: Recently, temozolomide, an oral alkylating chemotherapeutic agent, has been used successfully in cases of aggressive pituitary tumors. O⁶-methylguanine-DNA methyltransferase (MGMT) is a DNA repair protein that directly opposes the action of temozolomide.

Objectives: To study MGMT expression in a large cohort of pituitary tumors and determine whether MGMT expression is associated with response to temozolomide therapy in aggressive pituitary tumors.

Methods: Three cases of aggressive pituitary tumours treated with temozolomide therapy and 88 archived pituitary samples were studied. MGMT expression was assessed by immunohistochemistry. MGMT promoter methylation was studied by methylation-specific PCR (MSP), sequencing of MGMT was performed and loss of heterozygosity analysis undertaken.

Results: Low MGMT expression and MGMT promoter methylation were found in the pituitary tumors of the 2 patients who responded to temozolomide. Conversely, high MGMT expression was seen in the patient demonstrating a poor response to temozolomide. Eleven out of 88 archived tumor samples (13%) had low MGMT expression. Prolactinomas were more likely to have low MGMT expression compared with other pituitary tumor subtypes ($p < 0.001$). There was no significant difference in MGMT expression between invasive and non-invasive tumors, or between recurrent and non-recurrent tumors. A significant inverse correlation was found between MGMT expression and promoter methylation ($p = 0.003$).

Conclusion: MGMT expression as assessed by immunohistochemistry may predict response to temozolomide therapy in patients with aggressive pituitary tumors and thus guide more effective use of this agent. MGMT promoter methylation is likely to explain low MGMT expression in some, but not all, pituitary tumors.

Disclosure: Nothing to disclose

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MR Imaging of Rathke's Cleft Cysts

Jean-Francois Bonneville¹, Fabrice Bonneville², Clelia Billon-Grand¹, Alina David¹, Françoise Cattin¹

¹Jean Minjoz Hospital, Neuroradiology, Besancon, Doubs, France, ²Rangueil Hospital, Neuroradiology, Toulouse, Haute-Garonne, France

Purpose: To describe the various MR patterns of Rathke's cleft cysts (RCCs)

RCCs are frequent benign cystic sellar lesions characterized by a thin monolayer wall containing mucus-secreting goblets cells. Most RCC are small, intrasellar and asymptomatic and are considered as the most frequent incidentalomas in the sellar region. Intrasellar RCCs represent the main differential diagnosis of pituitary microadenomas. Larger cysts may compress adjacent structures and become symptomatic. Diagnosis is strongly suggested at MRI by the presence of a midline non-enhancing lesion located exactly between the anterior and posterior lobes of the pituitary gland: axial T1-weighted images without gadolinium injection are quite always the most informative sequence. RCCs show several variable MRI features depending on their content, serous or mucous. The MR signal is homogeneous with no fluid-fluid level; intracystic hyperproteic nodules presenting a hyposignal on T2-weighted images, can be observed. Coexisting microprolactinoma and RCC is not rare; in this condition, the RCC can be displaced or compressed by the microprolactinoma. Spontaneous evolution of RCC cyst is poorly known: RCCs can be stable, decrease or increase in volume; signal changes, sometimes relative to bleeding, have been reported. During pregnancy, an increase in volume is not unusual. Once diagnosis of RCC is made, MR and clinical follow-up is sufficient in incidental asymptomatic cysts.

Disclosure: Nothing to disclose

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The Clinical and Genetic Features of a Familial Isolated Pituitary Adenoma Family with an AIP Mutation Identified by Multiplex Ligation Probe Amplification

Harvinder Chahal¹, Michael Powell², Susana Igreja¹, Munayem Khan¹, Katie Guegan³, Sian Ellard⁴, VK Ajith Kumar⁴, Ashley Grossman¹, Marta Korbonits¹

¹Centre for Endocrinology, Barts and the London School of Medicine, London, United Kingdom, ²Department of Neurosurgery, National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom, ³Department of Molecular Genetics, Royal Devon and Exeter Foundation Trust, Exeter, United Kingdom, ⁴Clinical Genetics Department, Great Ormond Street Hospital, London, United Kingdom

Background: Recently, mutations in the AIP gene have been found to occur in patients with 'familial isolated pituitary adenoma' (FIPA). However, these mutations have been detected by conventional sequencing techniques which can miss large genomic deletions.

Objectives: To describe the clinical and genetic features of a FIPA family with a large genomic deletion in the AIP gene.

Subjects and methods: We report a FIPA family where four members were diagnosed with pituitary adenomas. Initial sequencing of the family using conventional sequencing revealed no mutations in the AIP gene. We carried out multiplex ligation probe amplification (MLPA) and immunohistochemical analysis for the AIP protein.

Results: The proband was diagnosed clinically and biochemically with acromegaly aged 18 years. MRI scanning showed a large macroadenoma, he underwent a transsphenoidal operation and histology was consistent with a somato-mammotroph adenoma. The proband's brother presented clinically and biochemically with a non-functioning adenoma. MRI scanning showed a large macroadenoma, he underwent a transsphenoidal operation and histology was consistent with a chromophobe adenoma. Postoperatively both brothers did not require any endocrine hormone replacement and currently have no evidence of disease recurrence. The proband's cousin was operated at the age of 27 years for a microadenoma which stained positive for growth hormone and prolactin. MLPA revealed a heterozygous AIP exon-2 deletion in the two brothers and immunohistochemical analysis of the three pituitary tumours revealed the presence of the AIP protein. Recently the proband's 17 year old sister had an MRI of the pituitary showing a 4mm adenoma, but currently she does not have any endocrine disease clinically or biochemically.

Conclusion: We present a FIPA family with four members being diagnosed with pituitary adenomas at a young age. An AIP mutation involving a whole exon deletion was only detected by the technique of MLPA, however, the AIP protein was still detectable by immunohistochemistry.

Disclosure: All authors have nothing to disclose

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Rathke Cleft Cysts – Results of a Multicenter Cross-Sectional Study on Diagnostics, Therapy and Prognosis in 14 Children and Adolescents

Hermann L Müller¹, Ursel Gebhardt¹, Rolf-Dieter Kortmann², Andreas Faldum³, Monika Warmuth-Metz⁴, Torsten Pietsch⁵, Niels Sörensen⁶

¹Klinikum Oldenburg gGmbH, Pediatrics, Oldenburg, Lower Saxony, Germany, ²University Hospital, Radiooncology, Leipzig, Saxony, Germany, ³University, IMBEI, Mainz, Rheinlandpfalz, Germany, ⁴University Hospital Neuroradiology, Würzburg, Bavaria, Germany, ⁵University Neuropathology, Bonn, Nordrheinwestfalen, Germany, ⁶Evangelisches Krankenhaus, Neurosurgery, Oldenburg, Lower Saxony, Germany

In HIT Endo 14 patients (8m/6f) with a Rathke cleft cyst (RCC) were recruited. RCC were compared to 117 patients (60m/57f) with childhood craniopharyngioma (CRA) recruited in KRANIOPHARYNGEOM 2000 and prospectively assessed for clinical manifestations, treatment and quality of survival (QoS). Histological diagnoses were assessed by a reference panel in all cases. RCC was diagnosed at an age of 10.2 yrs (3-15), CRA: 10.0 yrs (1-18). The localization of RCC was in 57% intrasellar, 14% extrasellar and 29% combined intra+extrasellar; CRA: 3% intrasellar, 23% extrasellar, 76% combined intra+extrasellar ($p < 0.01$). No differences between RCC and CRA were found in terms of duration of history, endocrine deficits, hydrocephalus, body mass index (BMI) and height at diagnosis and height at last evaluation. RCC patients presented with smaller masses than CRA patients ($p = 0.001$) and without hypothalamic involvement (69% in CRA; $p < 0.001$). Complete surgical resections were achieved in 46% RCC and 59% CRA. Local external irradiation was performed in 14% of RCC (1 pt after 4 relapses, 3 yrs after diagnosis; 1 pt after 2 relapses, 1.2 yrs after diagnosis) and 27% of CRA. We observed a 3-yr overall-survival of 1.00 and 0.97 in RCC and CRA, respectively. 3-yr event-free-survival rates were higher in RCC (0.82 ± 0.12) when compared to CRA (0.44 ± 0.06) ($p = 0.03$). The follow-up in CRA (3.1 yrs [0.1-7.1]) was influenced by a higher degree of obesity (BMI-SDS at last evaluation: 2.9 [-1.8-14.6]) when compared with RCC (follow-up: 3.3 yrs [0.1-14.7]; BMI-SDS: -0.1 [-1.4-5.9]) ($p = 0.001$). Differences in terms of QoS as measured by FMH questionnaire at the time of last evaluation did not reach significance. We conclude that radical resection is the therapy of first choice in RCC. Irradiation was effective in recurrent RCC. Due to the lack of hypothalamic involvement, obesity had no significant impact on QoS in RCC in contrast to CRA.

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Randomized Multicenter Trial on Patients with Childhood Craniopharyngioma (KRANIOPHARYNGEOM 2007) – Update after 18 Months of Recruitment

Hermann L Müller¹, Ursel Gebhardt¹, Sabine Schröder¹, Rolf-Dieter Kortmann², Andreas Faldum³, Monika Warmuth-Metz⁴, Torsten Pietsch⁵, Gabriele Calaminus⁶, Christoph Wiegand⁷, Niels Sörensen⁷

¹Klinikum Oldenburg gGmbH, Pediatrics, Oldenburg, Lower Saxony, Germany, ²University Hospital, Radiooncology, Leipzig, Saxony, Germany, ³University, IMBEI, Mainz, Rheinlandpfalz, Germany, ⁴University Hospital, Neuroradiology, Würzburg, Bavaria, Germany, ⁵University Hospital, Neuropathology, Bonn, Nordrheinwestfalen, Germany, ⁶University Hospital, Pediatric Oncology, Munster, Nordrheinwestfalen, Germany, ⁷Evangelisches Krankenhaus, Neurosurgery, Oldenburg, Lower Saxony, Germany

Despite high overall survival rates (92%) in patients with childhood craniopharyngioma (CP), health-related quality of life (QoL) is frequently impaired due to sequelae resulting from hypothalamic involvement. Based on the results of KRANIOPHARYNGEOM 2000 radical surgery is no appropriate treatment strategy in patients with hypothalamic involvement of CP. Furthermore, tumor progression and relapses are frequent and early events in CP patients. The analysis of event-free survival rates (EFS) in 117 prospectively evaluated patients with CP showed a high rate of early events in terms of tumor progression after incomplete resection (EFS: 0.31±0.07) and relapses after complete resection (EFS: 0.63±0.09) during the first three years of follow-up. Therefore, innovative treatment strategies are warranted for patients with hypothalamic involvement of CP after incomplete resection. Accordingly, in KRANIOPHARYNGEOM 2007 QoL, and survival rates in CP pts are analyzed after randomization of the time point of irradiation (XRT) after incomplete resection (immediate XRT versus XRT at progression of residual tumor). Up to now (03/09) 36 pts with CP were recruited in KRANIOPHARYNGEOM 2007 (22 pts in the randomization arm; 9 pts in the surveillance arm; 5 pts in the process of review of imaging). 9 of 22 pts were randomized. 13 pts could not be randomized due to parental decision (4 pts), insufficient organization (5 pts) and due to decision of the physician (4 pts). In conclusion, KRANIOPHARYNGEOM 2007 represents the first randomized trial in patients with CP. Aim of the study is to analyze the appropriate time point of XRT after incomplete resection in order to improve QoL in patients with hypothalamic involvement. The recruitment rate is high. However, the compliance to randomization has to be improved. Problems in the randomization process have been improved during the first year of recruitment. International recruitment of CP in KRANIOPHARYNGEOM 2007 will start in 2009.

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Xanthogranuloma of the Sellar Region – Results of a Multicenter Prospective Study on Diagnostics, Therapy and Prognosis in Children and Adolescents

Hermann L Müller¹, Ursel Gebhardt¹, Sabine Schröder¹, Rolf-Dieter Kortmann², Andreas Faldum³, Monika Warmuth-Metz⁴, Torsten Pietsch⁵, Gabriele Calaminus⁶, Christoph Wiegand⁷, Niels Sörensen⁷

¹Klinikum Oldenburg gGmbH, Pediatrics, Oldenburg, Lower Saxony, Germany, ²University Hospital, Radiooncology, Leipzig, Saxony, Germany, ³University, IMBEI, Mainz, Rheinlandpfalz, Germany, ⁴University Hospital, Neuroradiology, Würzburg, Bavaria, Germany, ⁵University, Neuropathology, Bonn, Nordrheinwestfalen, Germany, ⁶University Hospital, Pediatrics, Munster, Nordrheinwestfalen, Germany, ⁷Evangelisches Krankenhaus, Neurosurgery, Oldenburg, Lower Saxony, Germany

In KRANIOPHARYNGEOM 2000 117 patients with newly diagnosed childhood craniopharyngioma (CRA) from Germany, Austria and Switzerland were recruited between 2001 and 2007. Additionally, 14 patients with childhood xanthogranuloma (XTO) were included in our observational study. All patients were prospectively analyzed for clinical manifestations, treatment and risk factors for relapses. Histological diagnoses were assessed by a reference panel in all cases. Differences between the cohorts of XTO and CRA patients were not detectable for gender, age at diagnosis, severe endocrine deficits, functional capacity at last evaluation and height SDS and body mass index SDS at the time of diagnosis and at last evaluation. We observed a 3-year-OS and 3-year-EFS of 1.00 in patients with XTO in comparison with CRA patients (3-yrs-EFS: 0.63±0.09 after complete resection and 0.31±0.07 after incomplete resection). The localization of the sellar/parasellar mass was intrasellar in 8%/3%, extrasellar in 0%/23% and combined intra-+extrasellar in 92%/76% and hypothalamic involvement 46%/68% for patients with XTO and CRA, respectively. The median duration of history was 18 mo (1-96) in XTO and 5 mo (0.3-84) in CRA. A complete resection was achieved in 100% of XTO and 41% of CRA. Irradiation was performed in 27% of CRA patients and in none of XTO patients. Median tumour volume: 2.8 cm³ (0.3-9.2) in XTO and 13.5 cm³ (0.9-2.4) in CRA. Visual disturbances were less frequent observed in XTO patients (18%) when compared with CRA (60%). Hydrocephalus was observed none of the XTO patients (35% CRA). We conclude that the overall prognosis in terms of EFS rate, visual disturbances and hydrocephalus was better in XTO in comparison with CRA. XTO patients presented with smaller tumors and longer history. In contrast to the literature suprasellar extension and hypothalamic involvement in XTO was observed frequently. Surgical resection seems to be the treatment of choice in XTO.

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Meningiomas in Childhood and Adolescence – Prognosis in Relation to Histological Grade and Parasellar Localization

Hermann L Müller¹, Ursel Gebhardt¹, Sabine Schröder¹, Andreas Faldum², Monika Warmuth-Metz³, Torsten Pietsch⁴, Christoph Wiegand⁵, Niels Schröder⁵

¹Klinikum Oldenburg gGmbH, Department of Pediatrics, Oldenburg, Lower Saxony, Germany, ²University Mainz, IMBEI, Mainz, Rheinlandpfalz, Germany, ³University Hospital, Department of Neuroradiology, Würzburg, Bavaria, Germany, ⁴University Hospital, Institute of Neuropathology, Bonn, Nordrheinwestfalen, Germany, ⁵Evangelisches Krankenhaus, Department of Neurosurgery, Oldenburg, Lower Saxony, Germany

Meningioma (MG) are rare tumors during childhood. We analyzed the impact of treatment modalities and tumor localization on prognosis. 42 patients with childhood MG were included in our cross-sectional study (HIT-Endo). Pts with neurofibromatosis or MG as a second malignancy were excluded.

Median age at diagnosis of MG was 8.4 years (0.1-17.6 yrs). The histological diagnosis was confirmed by reference assessment in all pts (18 WHO I; 16 I/II; 3 III; 2 IV). The localizations were hemispheric in 25 pts, 6 optical tract, 5 parasellar and 2 cerebellar. Complete resection (CR) was achieved in 24 pts (19 I/II, 4 III/IV). Tumor progressions/relapses occurred in 11 of 19 pts after IR, in 10 of 24 pts after CR. Irradiation (XRT) was performed in 16 pts (38% after CR; 63% after incomplete resection [IR]), chemotherapy (XCH) in 6 pts (1 I/II after IR, 5 III/IV after CR). MG was non-responsive to XCH in 3 pts, in whom treatment response could be evaluated. 5-yrs-overall (OS) and event-free-survival rates (EFS) were lower ($p < 0.001/p < 0.05$) in III/IV (n=5; OS:0.27±0.23, EFS:0.40±0.22) in comparison with I/II (n=34; OS:0.97±0.3, EFS:0.48±0.11). 5-yrs-EFS in pts with WHO I/II was related to the degree of resection (CR: n=19, EFS:0.69±0.12; IR: n=15, EFS:0.34±0.15; $p < 0.05$). XRT had an impact on EFS in pts with I/II after IR (XRT after IR: n=8, 3-yrs EFS:0.83±0.15; no-XRT after IR: n=7, 3-yrs-EFS:0.33±0.26). The prognoses (OS/EFS) in 5 parasellar MG (1 I, 4 II) were comparable with I/II-MG of non-parasellar localization (1 complete remission, 3 stable disease; 1 progressive disease after surgery+XRT in 4 patients and multiple surgery in 1 patient).

For MG WHO I/II a radical surgical strategy and XRT were feasible. MG WHO III/IV had the poorest prognosis regardless of treatment factors such as the degree of resection, XRT or XCH. Parasellar localization had no significant impact on prognosis. Novel and effective strategies are warranted in childhood MG III/IV.

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Changing Expression of Pituitary erbB Receptor Tyrosine Kinases in Progression from Benign to Aggressive Nonfunctioning Adenomas

Odelia Cooper¹, Vivien Bonert¹, Kolja Wawrowsky¹, Shlomo Melmed¹

¹Cedars-Sinai Medical Center, Department of Medicine, Los Angeles, CA, United States

Introduction: We hypothesize that pituitary tumors progress from a noninvasive phenotype to a more aggressive one due to changes in levels of erbB receptor tyrosine kinase activities. We compared large, invasive nonfunctioning adenomas (NFAs) to small, noninvasive adenomas.

Methods: We evaluated 52 large NFAs and 22 small NFAs in an IRB approved human cohort analysis using immunohistochemistry and immunoblotting to test for EGFR, erbB2, and erbB3. Fisher's exact test was used for categorical variables and t-test and Mann-Whitney test used to compare means of continuous variables.

Results: In comparison to small NFAs, large NFAs presented with more invasion on MRI, higher median tumor diameter and postoperatively showed residual tumor and recurrences. Percent positive staining of tumor cells for large NFAs was 97 ± 10% for EGFR ($p = 0.0032$ vs small NFAs), 75 ± 28% for erbB2 ($p < 0.0001$), and 67 ± 32% for erbB3 ($p < 0.0001$) compared to 70 ± 39%, 27 ± 32%, and 15 ± 25% in small NFAs, respectively. erbB2 and erbB3 expression was more intense in large NFAs than in small NFAs ($p < 0.0042$, < 0.035 respectively). EGFR staining correlated with increasing tumor diameter ($p = 0.0123$) and cavernous sinus invasion ($p = 0.026$). erbB2 staining correlated with increasing tumor diameter ($p = 0.0128$), chiasm compression ($p = 0.02$), suprasellar invasion ($p = 0.0002$), cavernous sinus invasion ($p = 0.0003$), and extralobar spread ($p = 0.02$). erbB3 staining correlated with increasing tumor diameter ($p = .001$), chiasm compression ($p = 0.045$), cavernous sinus invasion ($p = 0.0019$), and residual tumor ($p = 0.0017$). Western blot confirmed expression of tumor EGFR, erbB2, and erbB3.

Discussion: Large NFAs had ~40% higher percentage of cells expressing EGFR, 1.7-fold higher erbB2, and 3.5-fold higher erbB3 than in small NFAs. These results suggest the potential for targeting erbB receptors with tyrosine kinase inhibitors for treating aggressive pituitary tumors.

Disclosure: Nothing to disclose for all authors.

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An International Collaborative Study of the Clinical Characteristics and Therapeutic Responses in 92 Pituitary Adenoma Patients with Mutations of the Aryl Hydrocarbon Receptor Interacting Protein Gene

A.F Daly¹, A. Beckers¹, The investigators of the FIPA Study Group¹

¹CHU de Liège, Endocrinology, Liège, Belgium

Background: Mutations in the AIP gene are associated with a predisposition to pituitary adenomas, which can occur in a proportion of patients with Familial Isolated Pituitary Adenomas (FIPA). The characteristics of patients with AIP mutation-related pituitary adenomas have not been studied in an organised manner in a large population.

Methods: Patients with pituitary adenomas and AIP mutations were identified by collaborating research groups worldwide. Demographic/disease characteristics and therapeutic management, including responses to neurosurgery, radiotherapy and somatostatin analogs (SSA), dopamine agonists (DA) were assessed using the same data collection system in all cases.

Results: We identified 92 patients with pituitary adenomas and AIP mutations; 64% were familial (FIPA) and 66% were males. There were 74 somatotropinomas, 11 prolactinomas, six non-secreting (NS) adenomas and one TSHoma. In the somatotropinoma group the mean age at diagnosis was 24.6 yr, with first symptoms occurring at 21.3 yr; 21 patients had gigantism. Somatotropinomas were large (mean diameter: 23.6mm) and only 6/94 (6.4%) of AIP-mutation associated tumors were microadenomas. Prolactinomas were macroadenomas in 10/11 cases (mean diameter: 32.8mm), 7/11 occurred in males and the mean age at diagnosis was 21.4 yr. Extension and invasion occurred in 52.6% and 40.0% of patients overall. Neurosurgery was performed in 61 somatotropinoma patients (12 had 2 surgeries, 2 had 3 surgeries); only 20 were cured with surgery alone. Radiotherapy was required in 25 somatotropinoma cases and 25/36 cases treated with SSA treatment did not experience GH and IGF-I control. Addition of pegvisomant led to control in 1 of 3 cases treated. Among prolactinomas, 5 required surgery (1 had 4 surgeries, and 2 required 2 surgeries), 2 patients required radiotherapy and DA resistance occurred in 3 cases.

Conclusion: This is the first study to comprehensively address the clinical features of large group of AIP mutation-related pituitary adenoma cases, a familial evidence of mutations was common. Tumors were large, occurred at a young age, had frequent invasion/extension and there was evidence of poor success rates with surgery and medical therapy.

Disclosure: Nothing to disclose.

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Childhood Pituitary Adenoma – International Registry of Children and Adolescents from Germany, Austria and Switzerland (HIT-Endo)

Hermann L Müller¹, Ursel Gebhardt¹, Sabine Schröder¹, Rolf-Dieter Kortmann², Peter Kaatsch³, Monika Warmuth-Metz⁴,
Torsten Pietsch⁵, Bonn, Christoph Wiegand⁶, Niels Sörensen⁶

¹Klinikum Oldenburg gGmbH, Department of Pediatrics, Oldenburg, Lower Saxony, Germany, ²University Department of Radiooncology, Leipzig, Saxony, Germany, ³German Cancer Registry at IMBEI, University, Mainz, Rheinlandpfalz, Germany, ⁴University Department of Neuroradiology, Würzburg, Bavaria, Germany, ⁵University Institute of Neuropathology, Bonn, Nordrheinwestfalen, Germany, ⁶Evangelisches Krankenhaus, Department of Neurosurgery, Oldenburg, Lower Saxony, Germany

Cases of childhood pituitary adenoma are systematically documented by the German Paediatric Cancer Registry in accordance with international guidelines and recruited in a registry. In parallel to the surveillance study KRANIOPHARYNGEOM 2000 and the randomized prospective trial KRANIOPHARYNGEOM 2007 between 1997 and 2007 twenty-nine German, Austrian and Swiss patients with childhood pituitary adenoma were recruited in the HIT-Endo registry. Recruited patients with childhood pituitary adenoma were analyzed for the secreting type of adenoma and the chosen therapy based on the patients' records and the registration information.

Twenty-nine patients (16m/13f) were registered with a median age of 13 years (range: 1-18 years) at the time of diagnosis. Based on the records, visual impairment was a clinical manifestation at diagnosis in 16 patients (55%). In 13 patients treated surgically, a complete resection could be achieved in 7 patients, incomplete resection in 6 patients, no surgery in 10 patients (in 6 patients no information was available). One patient received local external irradiation, 22 patients were not irradiated (no information in 6 patients). Fifteen patients were diagnosed with a secreting adenoma, 8 patients with a non-secreting type of adenoma (no information was available in 6 patients). The patterns of hormonal secretion were: 2 patients GH, 3 prolactin, 1 prolactin + ACTH + GH; 2 prolactin + GH, 5 ACTH, 1 TSH, 1 ACTH + GH.

The completeness of data acquisition has to be improved, in order to draw valid conclusions on treatment and prognosis in patients with childhood pituitary adenoma. In regard to the rareness of the disease, international cooperation in registration of patients and data evaluation is warranted.

Disclosure: Supported by Deutsche Kinderkrebsstiftung, Bonn, Germany

Sandostatin LAR® Depot

(octreotide acetate for injectable suspension)

Initial U.S. Approval: 1988

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

Sandostatin LAR Depot 10 mg, 20 mg and 30 mg is indicated in patients in whom initial treatment with Sandostatin Injection has been shown to be effective and tolerated.

1.1 Acromegaly

Long-term maintenance therapy in acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal [see *Clinical Studies (14) and Dosage and Administration (2) in the full prescribing information*].

1.2 Carcinoid Tumors

Long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.

1.3 Vasoactive Intestinal Peptide Tumors (VIPomas)

Long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors.

1.4 Important Limitations of Use

In patients with carcinoid syndrome and VIPomas, the effect of Sandostatin Injection and Sandostatin LAR Depot on tumor size, rate of growth and development of metastases, has not been determined.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Cholelithiasis and Gallbladder Sludge

Sandostatin may inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities or sludge. Patients should be monitored periodically [see *Adverse Reactions (6)*].

5.2 Hyperglycemia and Hypoglycemia

Octreotide alters the balance between the counter-regulatory hormones, insulin, glucagon, and growth hormone, which may result in hypoglycemia or hyperglycemia. Blood glucose levels should be monitored when Sandostatin LAR treatment is initiated, or when the dose is altered. Anti-diabetic treatment should be adjusted accordingly [see *Adverse Reactions (6)*].

5.3 Thyroid Function Abnormalities

Octreotide suppresses the secretion of thyroid stimulating hormone, which may result in hypothyroidism. Baseline and periodic assessment of thyroid function (TSH, total and/or free T₄) is recommended during chronic octreotide therapy [see *Adverse Reactions (6)*].

5.4 Cardiac Function Abnormalities

In both acromegalic and carcinoid syndrome patients, bradycardia, arrhythmias and conduction abnormalities have been reported during octreotide therapy. Other EKG changes were observed such as QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease. Dose adjustments in drugs such as beta blockers that have bradycardia effects may be necessary. In one acromegalic patient with severe congestive heart failure, initiation of Sandostatin Injection therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive rechallenge [see *Adverse Reactions (6)*].

5.5 Nutrition

Octreotide may alter absorption of dietary fats.

Depressed vitamin B₁₂ levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy, and monitoring of vitamin B₁₂ levels is recommended during therapy with Sandostatin LAR Depot.

Octreotide has been investigated for the reduction of excessive fluid loss from the G.I. tract in patients with conditions producing such a loss. If such patients are receiving total parenteral nutrition (TPN), serum zinc may rise excessively when the fluid loss is reversed. Patients on TPN and octreotide should have periodic monitoring of zinc levels.

5.6 Monitoring: Laboratory Tests

Laboratory tests that may be helpful as biochemical markers in determining and following patient response depend on the specific tumor. Based on diagnosis, measurement of the following substances may be useful in monitoring the progress of therapy [see *Dosage and Administration (2.0) in the full prescribing information*].

Acromegaly: Growth Hormone, IGF-1 (somatomedin C)

Carcinoid: 5-HIAA (urinary 5-hydroxyindole acetic acid), plasma serotonin, plasma Substance P

VIPoma: VIP (plasma vasoactive intestinal peptide) baseline and periodic total and/or free T₄ measurements should be performed during chronic therapy

5.7 Drug Interactions

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine [see *Drug Interactions (7.2)*].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice.

6.1.1 Acromegaly

The safety of Sandostatin LAR in the treatment of acromegaly has been evaluated in 3 phase 3 studies in 261 patients, including 209 exposed for 48 weeks and 96 exposed for greater than 108 weeks. Sandostatin LAR was studied primarily in a double-blind, cross-over manner. Patients on subcutaneous Sandostatin Injection were switched to the LAR formulation followed by an open-label extension. The population age range was 14-81 years old and 53% were female. Approximately 35% of these acromegaly patients had not been treated with surgery and/or radiation. Most patients received a starting dose of 20 mg every 4 weeks intramuscularly. Dose was up or down titrated based on efficacy and tolerability to a final dose between 10-60 mg every 4 weeks. Table 1 below reflects adverse events from these studies regardless of presumed causality to study drug.

Table 1. Adverse Events Occurring in ≥10% of Acromegalic Patients in the Phase 3 Studies

WHO Preferred Term	Phase 3 Studies (Pooled) Number (%) of Subjects with AE's 10 mg/20 mg/30 mg (n=261) n (%)
Diarrhea	93 (35.6)
Abdominal Pain	75 (28.7)
Flatulence	66 (25.3)
Influenza-Like Symptoms	52 (19.9)
Constipation	46 (17.6)
Headache	40 (15.3)
Anemia	40 (15.3)
Injection Site Pain	36 (13.8)
Cholelithiasis	35 (13.4)
Hypertension	33 (12.6)
Dizziness	30 (11.5)
Fatigue	29 (11.1)

The safety of Sandostatin LAR in the treatment of acromegaly was also evaluated in a post-marketing randomized phase 4 study. 104 patients were randomized to either pituitary surgery or 20 mg of Sandostatin LAR. All the patients were treatment naïve ('de novo'). Cross over was allowed according to treatment response and a total of 76 patients were exposed to Sandostatin LAR. Approximately half of the patients initially randomized to Sandostatin LAR were exposed to Sandostatin LAR up to 1 year. The population age range was between 20-76 years old and 45% were female, 93% were Caucasian, and 1% Black. The majority of these patients were exposed to 30 mg every 4 weeks. Table 2 below reflects the adverse events occurring in this study regardless of presumed causality to study drug.

Table 2. Adverse Events Occurring in ≥10% of Acromegalic Patients in Phase 4 Study

WHO Preferred Term	Phase 4 Study SAS LAR N=76 n (%)	Phase 4 Study Surgery N=64 n (%)
Diarrhea	36 (47.4)	2 (3.1)
Cholelithiasis	29 (38.2)	3 (4.7)
Abdominal Pain	19 (25.0)	2 (3.1)
Nausea	12 (15.8)	5 (7.8)
Alopecia	10 (13.2)	5 (7.8)
Injection Site Pain	9 (11.8)	0
Abdominal Pain Upper	8 (10.5)	0
Headache	8 (10.5)	6 (9.4)
Epistaxis	0	7 (10.9)

Gallbladder Abnormalities

Single doses of Sandostatin Injection have been shown to inhibit gallbladder contractility and decrease bile secretion in normal volunteers. In clinical trials with Sandostatin Injection (primarily patients with acromegaly or psoriasis) in patients who had not previously received octreotide, the incidence of biliary tract abnormalities was 63% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received Sandostatin Injection for 12 months or longer was 52%. The incidence of gallbladder abnormalities did not appear to be related to age, sex or dose but was related to duration of exposure.

In clinical trials 52% of acromegalic patients, most of whom received Sandostatin LAR Depot for 12 months or longer, developed new biliary abnormalities including gallstones, microlithiasis, sediment, sludge and dilatation. The incidence of new cholelithiasis was 22%, of which 7% were microstones.

Across all trials, a few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during octreotide therapy or following its withdrawal. One patient developed ascending cholangitis during Sandostatin Injection therapy and died. Despite the high incidence of new gallstones in patients receiving octreotide, 1% of patients developed acute symptoms requiring cholecystectomy.

Glucose Metabolism - Hypoglycemia/Hyperglycemia

In acromegaly patients treated with either Sandostatin Injection or Sandostatin LAR Depot, hypoglycemia occurred in approximately 2% and hyperglycemia in approximately 15% of patients [see Warnings and Precautions (5)].

Hypothyroidism

In acromegaly patients receiving Sandostatin Injection, 12% developed biochemical hypothyroidism, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Sandostatin Injection. In acromegalics treated with Sandostatin LAR Depot hypothyroidism was reported as an adverse event in 2% and goiter in 2%. Two patients receiving Sandostatin LAR Depot required initiation of thyroid hormone replacement therapy [see Warnings and Precautions (5)].

Cardiac

In acromegalics, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin Injection therapy. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease [see Warnings and Precautions (5)].

Gastrointestinal

The most common symptoms are gastrointestinal. The overall incidence of the most frequent of these symptoms in clinical trials of acromegalic patients treated for approximately 1 to 4 years is shown in Table 3.

Table 3. Number (%) of Acromegalic Patients with Common G.I. Adverse Events

Adverse Event	Sandostatin Injection S.C. Three Times Daily n=114		Sandostatin LAR Depot Every 28 Days n=261	
	n	%	n	%
Diarrhea	66	(57.9)	95	(36.4)
Abdominal Pain or Discomfort	50	(43.9)	76	(29.1)
Nausea	34	(29.8)	27	(10.3)
Flatulence	15	(13.2)	67	(25.7)
Constipation	10	(8.8)	49	(18.8)
Vomiting	5	(4.4)	17	(6.5)

Only 2.6% of the patients on Sandostatin Injection in U.S. clinical trials discontinued therapy due to these symptoms. No acromegalic patient receiving Sandostatin LAR Depot discontinued therapy for a G.I. event.

In patients receiving Sandostatin LAR Depot the incidence of diarrhea was dose related. Diarrhea, abdominal pain, and nausea developed primarily during the first month of treatment with Sandostatin LAR Depot. Thereafter, new cases of these events were uncommon. The vast majority of these events were mild-to-moderate in severity.

In rare instances gastrointestinal adverse effects may resemble acute intestinal obstruction, with progressive abdominal distention, severe epigastric pain, abdominal tenderness, and guarding.

Dyspepsia, steatorrhea, discoloration of feces, and tenesmus were reported in 4%-6% of patients.

In a clinical trial of carcinoid syndrome, nausea, abdominal pain, and flatulence were reported in 27%-38% and constipation or vomiting in 15%-21% of patients treated with Sandostatin LAR Depot. Diarrhea was reported as an adverse event in 14% of patients but since most of the

patients had diarrhea as a symptom of carcinoid syndrome, it is difficult to assess the actual incidence of drug-related diarrhea.

Pain at the Injection Site

Pain on injection, which is generally mild-to-moderate, and short-lived (usually about 1 hour) is dose related, being reported by 2%, 9%, and 11% of acromegalics receiving doses of 10 mg, 20 mg and 30 mg, respectively, of Sandostatin LAR Depot. In carcinoid patients, where a diary was kept, pain at the injection site was reported by about 20%-25% at a 10-mg dose and about 30%-50% at the 20-mg and 30-mg dose.

Antibodies to Octreotide

Studies to date have shown that antibodies to octreotide develop in up to 25% of patients treated with octreotide acetate. These antibodies do not influence the degree of efficacy response to octreotide; however, in two acromegalic patients who received Sandostatin Injection, the duration of GH suppression following each injection was about twice as long as in patients without antibodies. It has not been determined whether octreotide antibodies will also prolong the duration of GH suppression in patients being treated with Sandostatin LAR Depot.

6.1.2 Carcinoid and VIPomas

The safety of Sandostatin LAR in the treatment of carcinoid tumors and VIPomas has been evaluated in one phase 3 study. Study 1 randomized 93 patients with carcinoid syndrome to Sandostatin LAR 10 mg, 20 mg or 30 mg in a blind fashion or to open label Sandostatin Injection subcutaneously. The population age range was between 25-78 years old and 44% were female, 95% were Caucasian and 3% Black. All the patients had symptom control on their previous Sandostatin subcutaneous treatment. Eighty patients finished the initial 24 weeks of Sandostatin exposure in study 1. In study 1, comparable numbers of patients were randomized to each dose. Table 4 below reflects the adverse events occurring in >15% of patients regardless of presumed causality to study drug.

Table 4. Adverse Events Occurring in ≥15% of Carcinoid Tumor and VIPoma Patients in Study 1

WHO Preferred Term	Study 1 Number (%) of Subjects with AE's (n=93)			
	Sc N=26	10 mg N=22	20 mg N=20	30 mg N=25
Abdominal Pain	8 (30.8)	8 (35.4)	2 (10.0)	5 (20.0)
Arthropathy	5 (19.2)	2 (9.1)	3 (15.0)	2 (8.0)
Back Pain	7 (26.9)	6 (27.3)	2 (10.0)	2 (8.0)
Dizziness	4 (15.4)	4 (18.2)	4 (20.0)	5 (20.0)
Fatigue	3 (11.5)	7 (31.8)	2 (10.0)	2 (8.0)
Flatulence	3 (11.5)	2 (9.1)	2 (10.0)	4 (16.0)
Generalized Pain	4 (15.4)	2 (9.1)	3 (15.0)	1 (4.0)
Headache	5 (19.2)	4 (18.2)	6 (30.0)	4 (16.0)
Musculoskeletal Pain	4 (15.4)	0	1 (5.0)	0
Myalgia	0	4 (18.2)	1 (5.0)	1 (4.0)
Nausea	8 (30.8)	9 (40.9)	6 (30.0)	6 (24.0)
Pruritus	0	4 (18.2)	0	0
Rash	1 (3.8)	0	3 (15.0)	0
Sinusitis	4 (15.4)	0	1 (5.0)	3 (12.0)
URTI	6 (23.1)	4 (18.2)	2 (10.0)	3 (12.0)
Vomiting	3 (11.5)	0	0	4 (16.0)

Gallbladder Abnormalities

In clinical trials 62% of malignant carcinoid patients who received Sandostatin LAR Depot for up to 18 months developed new biliary abnormalities including jaundice, gallstones, sludge and dilatation. New gallstones occurred in a total of 24% of patients.

Glucose Metabolism - Hypoglycemia/Hyperglycemia

In carcinoid patients, hypoglycemia occurred in 4% and hyperglycemia in 27% of patients treated with Sandostatin LAR Depot [see Warnings and Precautions (5)].

Hypothyroidism

In carcinoid patients, hypothyroidism has only been reported in isolated patients and goiter has not been reported [see Warnings and Precautions (5)].

Cardiac

Electrocardiograms were performed only in carcinoid patients receiving Sandostatin LAR Depot. In carcinoid syndrome patients sinus bradycardia developed in 19%, conduction abnormalities occurred in 9%, and arrhythmias developed in 3%. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease [see Warnings and Precautions (5)].

Other Clinical Studies Adverse Events

Other clinically significant adverse events (relationship to drug not established) in acromegalic and/or carcinoid syndrome patients receiving

Sandostatin LAR Depot were malignant hyperpyrexia, cerebral vascular disorder, rectal bleeding, ascites, pulmonary embolism, pneumonia and pleural effusion.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during the post-approval use of Sandostatin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Myocardial infarction has been observed in the post-marketing setting, mainly in patients with cardiovascular risk factors. Hypoadrenalism has been reported in some reports in patients 18 months of age and under.

Additional events reported in the post-marketing setting include anaphylactoid reactions, including anaphylactic shock, cardiac arrest, renal failure, renal insufficiency, convulsions, atrial fibrillation, aneurysm, hepatitis, increased liver enzymes, gastrointestinal hemorrhage, pancreatitis, pancytopenia, thrombocytopenia, arterial thrombosis of the arm, retinal vein thrombosis, intracranial hemorrhage, hemiparesis, paresis, deafness, visual field defect, aphasia, scotoma, status asthmaticus, pulmonary hypertension, diabetes mellitus, intestinal obstruction, peptic/gastric ulcer, appendicitis, creatinine increased, CK increased, arthritis, joint effusion, pituitary apoplexy, breast carcinoma, suicide attempt, paranoia, migraines, urticaria, facial edema, generalized edema, hematuria, orthostatic hypotension, Raynaud's syndrome, glaucoma, pulmonary nodule, pneumothorax aggravated, cellulitis, Bell's palsy, diabetes insipidus, gynecomastia, galactorrhea, gallbladder polyp, fatty liver, abdomen enlarged, libido decrease and petechiae.

7 DRUG INTERACTIONS

7.1 Cyclosporine

Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

7.2 Insulin and Oral Hypoglycemic Drugs

Octreotide inhibits the secretion of insulin and glucagon. Therefore, blood glucose levels should be monitored when Sandostatin LAR treatment is initiated or when the dose is altered and anti-diabetic treatment should be adjusted accordingly.

7.3 Bromocriptine

Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine.

7.4 Other Concomitant Drug Therapy

Concomitant administration of bradycardia-inducing drugs (e.g., beta blockers) may have an additive effect on the reduction of heart rate associated with octreotide. Dose adjustments of concomitant medication may be necessary.

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs.

7.5 Drug Metabolism Interactions

Limited published data indicate that somatostatin analogs may decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quinidine, terfenadine) should therefore be used with caution.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Reproduction studies have been performed in rats and rabbits at doses up to 16 times the highest recommended human dose and have revealed no evidence of harm to the fetus due to octreotide. However, because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed [see *Nonclinical Toxicology (13.2) in the full prescribing information*].

8.3 Nursing Mothers

It is not known whether octreotide is excreted into human milk. Because many drugs are excreted in human milk, caution should be exercised when Sandostatin LAR Depot is administered to a nursing woman.

8.4 Pediatric Use

In pediatric patients with hypothalamic obesity, the mean octreotide concentration after 6 doses of 40-mg Sandostatin LAR Depot administered by IM injection every four weeks was approximately 3 ng/mL. Steady-state concentration was achieved after 3 injections of a 40-mg dose.

The efficacy and safety of Sandostatin LAR Depot were examined in a randomized, double-blind, placebo-controlled six-month study in 60 pediatric patients aged 6-17 years with hypothalamic obesity resulting from

cranial insult. Mean BMI increased 0.1 kg/m² in Sandostatin LAR Depot-treated subjects compared to 0.0 kg/m² in saline control-treated subjects. Diarrhea occurred in 11 of 30 (37%) patients treated with Sandostatin LAR Depot. No unexpected adverse events were observed. However, with Sandostatin LAR Depot 40 mg once a month, the incidence of new cholelithiasis in this pediatric population (33%) was higher than that seen in other adult indications such as acromegaly (22%) or malignant carcinoid syndrome (24%), where Sandostatin LAR Depot was 10 to 30 mg once a month.

8.5 Geriatric Use

Clinical studies of Sandostatin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

In patients with renal failure requiring dialysis, the starting dose should be 10 mg. This dose should be up titrated based on clinical response and speed of response as deemed necessary by the physician. In patients with mild, moderate or severe renal impairment there is no need to adjust the starting dose of Sandostatin. The maintenance dose should be adjusted thereafter based on clinical response and tolerability as in non-renal patients [see *Clinical Pharmacology (12) in the full prescribing information*].

8.7 Hepatic Impairment - Cirrhotic Patients

In patients with established liver cirrhosis, the starting dose should be 10 mg. This dose should be up titrated based on clinical response and speed of response as deemed necessary by the physician. Once at a higher dose, patient should be maintained or dose adjusted based on response and tolerability as in any non-cirrhotic patients [see *Clinical Pharmacology (12) in the full prescribing information*].

16 HOW SUPPLIED/STORAGE AND HANDLING

Sandostatin LAR Depot is available in single-use kits containing a 5-mL vial of 10 mg, 20 mg or 30 mg strength, a syringe containing 2.5 mL of diluent, two sterile 1½" 19 gauge needles, and two alcohol wipes. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

Drug Product Kits

10 mg kit.....	NDC 0078-0340-61
20 mg kit.....	NDC 0078-0341-61
30 mg kit.....	NDC 0078-0342-61
Demonstration kit.....	NDC 0078-9342-61

For prolonged storage, Sandostatin LAR Depot should be stored at refrigerated temperatures between 2°C and 8°C (36°F-46°F) and protected from light until the time of use. Sandostatin LAR Depot drug product kit should remain at room temperature for 30-60 minutes prior to preparation of the drug suspension. However, after preparation the drug suspension must be administered immediately.

T2008-22
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Sandostatin LAR® Depot vials are manufactured by:
Sandoz GmbH, Schafftenau, Austria
(Subsidiary of Novartis Pharma AG, Basle, Switzerland)

The diluent syringes are manufactured by:
Solvay Pharmaceuticals B.V.
Olst, The Netherlands

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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ANNOUNCING: The Nurse Home Injection Program For eligibility, call 1-888-LAR-4759

For the long-term treatment of acromegaly, Sandostatin LAR® provides...

POWERFUL EFFICACY, UNPARALLELED EVIDENCE



Proven long-term efficacy in acromegaly.¹

Backed by over **600,000** patient-years of experience*^{†2}:

■ **57%-68%** of patients experienced both GH <2.5 ng/mL + IGF-1 normalization^{‡1,3}

Now the only somatostatin analogue proven to shrink tumors in acromegaly.¹

■ **36%** median tumor shrinkage achieved in previously untreated acromegalic patients at Week 48 (n=94)^{1,2}

– Greater than **20%** median tumor shrinkage at Week 24 (N=143)^{§1}

■ No patient experienced an increase in tumor volume while on treatment with Sandostatin LAR®⁴

Sandostatin LAR® Depot (octreotide acetate for injectable suspension) is indicated for long-term maintenance therapy in acromegalic patients for whom medical treatment is appropriate and who have been shown to respond to and can tolerate immediate release Sandostatin® (octreotide acetate) Injection. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal. Sandostatin LAR® Depot can be used in patients who have had an inadequate response to surgery or in those for whom surgical resection is not an option. It may also be used in patients who have received radiation and have had an inadequate therapeutic response.

Important Safety Information¹:

As with immediate release Sandostatin® Injection, the most frequently reported drug-related adverse events were biliary disorders (52%), gastrointestinal disorders (7% to 36%), and injection-site pain (2% to 11%). Hypoglycemia (2%), hyperglycemia (15%), and hypothyroidism (2%) have been reported. While not measured in acromegalic patients receiving Sandostatin LAR® Depot, ECG changes have been reported in patients receiving immediate release Sandostatin® Injection; the degree to which these abnormalities are related to octreotide acetate is not clear, as many acromegalics have cardiovascular disease.

Please see brief summary of Prescribing Information on adjacent page.

References: 1. Sandostatin LAR® Depot [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2008. 2. Data on file, Novartis Pharmaceuticals. 3. Cozzi R, Attanasio R, Montini M, et al. Four-year treatment with octreotide-long-acting repeatable in 100 acromegalic patients: predictive value of short-term results? *J Clin Endocrinol Metab.* 2003;88:3090-3098. 4. Mercado M, Borges F, Bouterfa H. A prospective, multicenter study to investigate the efficacy, safety and tolerability of octreotide LAR® (long-acting repeatable octreotide) in the primary therapy of patients with acromegaly. *Clin Endocrinol (Oxf).* 2007;66:859-868.

*Combined use of immediate release Sandostatin® Injection and Sandostatin LAR® Depot from all approved indications.

[†] Includes both ongoing and completed trials from all approved indications.

[‡] Range reflects results derived from pivotal trials and long-term follow-up data.

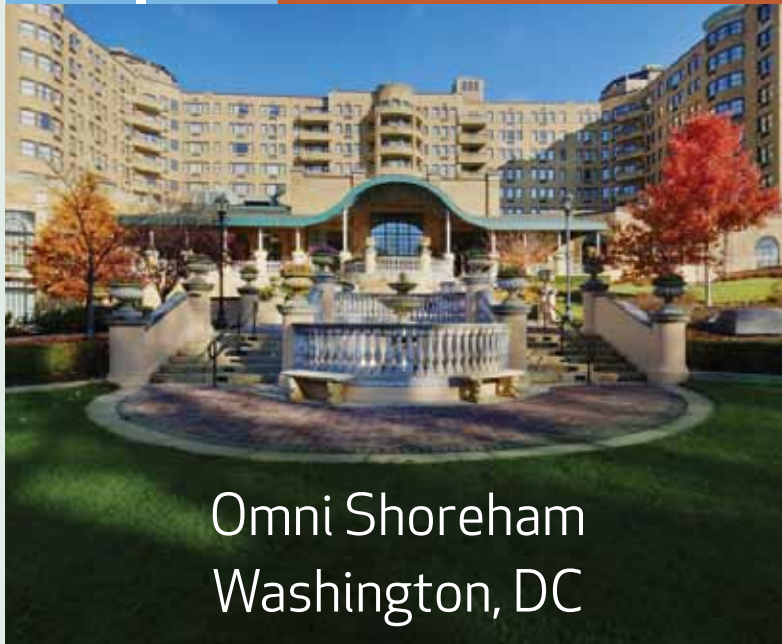
[§] Reduction in tumor size was demonstrated in 2 open-label studies (N=143).

 **Sandostatin LAR® Depot**
(octreotide acetate for injectable suspension)

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VA Medical Center
423 East 23rd Street
Room 16048aW
New York, NY 10010