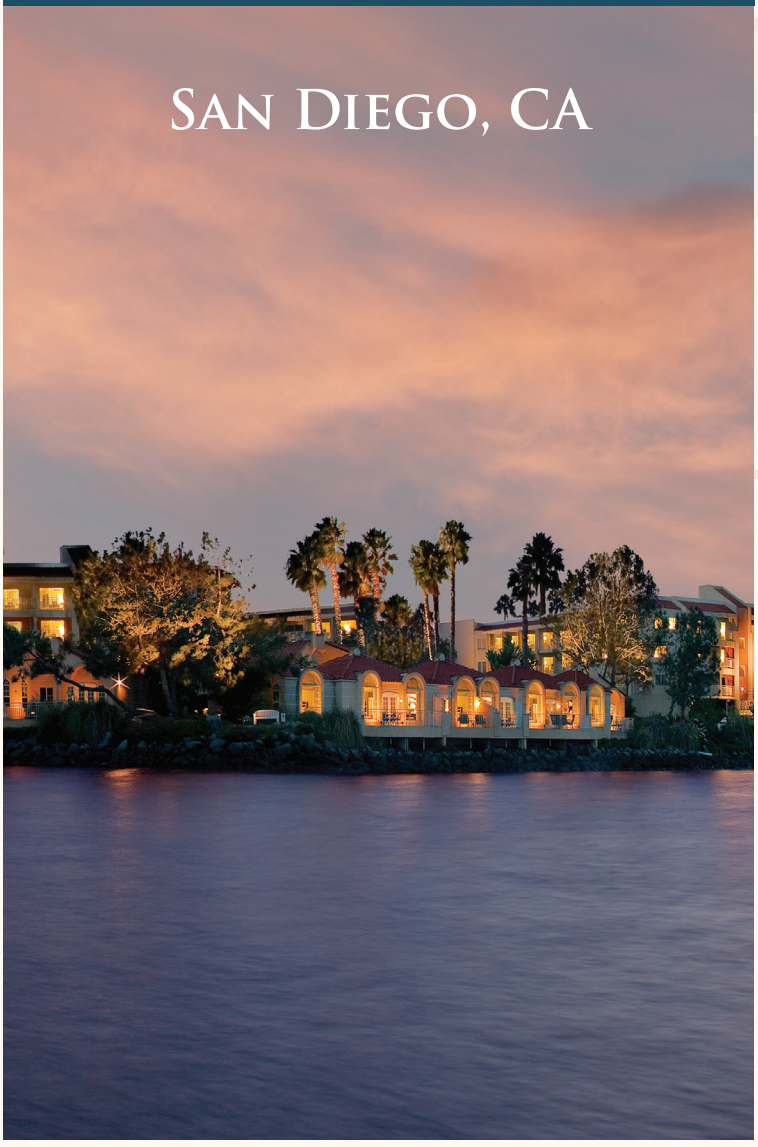
The Pituitary Society
presents the

14th FOURTEENTH INTERNATIONAL PITUITARY CONGRESS

MARCH 2 - 4, 2015



The 14th International Pituitary Congress is supported by:

Platinum Sponsor

Novartis

UNRESTRICTED EDUCATIONAL GRANTS PROVIDED BY

Gold Level Supporter

Ipsen

Silver Level Supporters

NovoNordisk

Pfizer

Corcept Therapeutics

PROGRAM AND ABSTRACTS

The Pituitary Society
Officers & Board Of Directors (2014-2015)

OFFICERS:

President
Ariel Barkan
Ann Arbor, MI, USA

President-elect
Ashley Grossman
Oxford, UK

International Relations
Felipe F. Casanueva
Santiago de Compostela, Spain

Secretary-Treasurer
David L. Kleinberg
New York, NY, USA

Program Co-Director
Anne Klibanski
Boston, MA, USA

Editor-in-Chief, Pituitary
Program Co-Director
Shlomo Melmed
Los Angeles, CA, USA

Senior Executive Director (ex-officio)
Mary Lee Vance
Charlottesville, VA, USA

BOARD OF DIRECTORS:

Paolo Beck-Peccoz
Milan, Italy

Cesar Luiz Boguszewski
Curitiba, Paraná, Brazil

Vivien Bonert
Los Angeles, CA, USA

Andrea Giustina
Brescia, Italy

Stephan Petersenn
Hamburg, Germany

Roberto Salvatori
Baltimore, MD, USA

Christian Strasburger
Berlin, Germany

PITUITARY EDITORS:

Ariel Barkan
Ann Arbor, MI, USA

Nienke Biermasz
Leiden, The Netherlands

Andrea Giustina
Brescia, Italy

John Wass
Oxford, UK

THE PITUITARY SOCIETY

Welcome

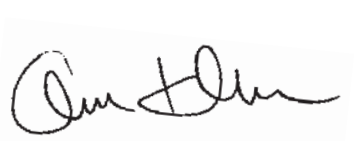
The Fourteenth International Pituitary Congress will present an exciting group of member and guest international experts in pituitary problems. It will include distinguished clinicians and clinical researchers, fellows in training, and experts in basic science. As usual, we will present cutting edge 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.

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

Please note our corporate partners who provide essential support for this meeting. We gratefully acknowledge their continued generous support.

Welcome again to two days of excellent science and companionship!

The Program Organizing Committee



Anne Klibanski *(Co-Chair)*

Shlomo Melmed *(Co-Chair)*

Program Committee:
Nienke Biermasz -The Netherlands
Beverly MK Biller - USA
Marcello Bronstein - Brazil
William Farrell - UK
Ursula Kaiser - USA
John Kopchick - USA
John Newell-Price - UK
Ron Rosenfeld - USA

Symposium Schedule

MONDAY, MARCH 2, 2015		
OPENING PLENARY LECTURES *Co-Chairs: Ariel Barkan and Mark Molitch*		
7:00 PM	Prolactin Receptor Mutations	*Rajesh Thakker*
7:30	GH as a Metabolic Hormone	*Rhonda Kineman*
SOCIAL EVENT		
8:00	Welcome Reception	
TUESDAY, MARCH 3, 2015		
7:30 AM	Continental Breakfast	
ACROMEGALY *Chair: Nienke Biermasz*		
8:30	Oral Octreotide Therapy of Acromegaly	*Vera Popovic*
8:50	Acromegaly Effects on Bone Metabolism and the Musculoskeletal System	*Kim Claessen*
9:10	What Can We Learn by Measuring Circulating GH Rhythms in Acromegaly?	*Antônio Ribeiro-Oliveira Jr*
9:30	Evidence Based Guidelines in Acromegaly: Limitations and Utility	*Mônica Gadelha and Peter Trainer*
10:00	Coffee Break & Poster Session	
GROWTH HORMONE - JOINT GRS SESSION *Chair: John Kopchick*		
10:45	GH Regulation of Electrolyte Balance	*Peter Kamenický*
11:05	GH-Induced Signaling in Human Muscle	*Jens Otto Jørgensen*
11:25	rhGH by Athletes: Is the Evidence Valid?	*Richard Holt*
11:45	Differential Effects of GH on White Adipose Tissue	*Darlene Berryman*
MEET THE PROFESSOR CONCURRENT WORKSHOPS (You will be able to attend two sessions)		
12:15-2:15 PM	Aggressive Pituitary Tumors or Localized Pituitary Carcinomas	*Luis V. Syro*
	Determination of Remission after Surgery for Cushing's Disease	*Michael Buchfelder and Brooke Swearingen*
	How Do I Interpret GH and IGF1 Assays?	*Martin Bidlingmaier*
	Pituitary Disorders in Pregnancy	*Züleyha Karaca*
	Cyclic Cushing's Syndrome	*Nicholas Tritos*
	Use of Genomics in Elucidating Puberty	*Nelly Pitteloud*
	What's the Latest on Endocrine Effects of Traumatic Brain Injury?	*Christopher Thompson*

Continued on page 3

Symposium Schedule *Continued from page 2*

PITUITARY TUMORS *Chair: John Newell-Price*		
2:15	**Management of Nelson's Syndrome and Invasive Corticotroph Tumors**	*Kalmon Post*
2:35	**Macroprolactinemia Revisited**	*Andrea Glezer*
2:55	**Targeted Therapy for Aggressive Pituitary Tumors – What are the Options? A Dual Perspective**	*Odelia Cooper and Niki Karavitaki*
3:25	**Coffee Break & Poster Session**	
ROUND TABLE DISCUSSION *Chair: Beverly MK Biller*		
4:15	**Critical Comparisons of Medical Therapies for Cushing's Disease** **Pasireotide** **Mifepristone** **Cabergoline** **Adrenal Synthesis-inhibitors**	*Anna Maria Colao* *Maria Fleseriu* *Jérôme Bertherat* *Xavier Bertagna*
5:30	**Poster Session**	
SOCIAL EVENTS		
6:30	**Congress Reception & Dinner**	
WEDNESDAY, MARCH 4, 2015		
7:30 AM	**Continental Breakfast**	
PITUITARY TRANSLATIONAL BIOLOGY *Chair: William Farrell*		
8:30	**Puberty Mechanisms**	*Ana Paula Abreu Metzger*
8:50	**Mechanisms for Prolactin Regulation of Reproduction**	*Nadine Binart*
9:10	**Pituitary Tumor Stem Cells**	*Cynthia-Lillian Andoniadou*
9:30	**Acquired Adult Hypopituitarism**	*Thierry Brue*
9:50	**Coffee Break & Poster Session**	
HOT TOPICS *Co-Chairs: Marcello Bronstein and Ursula Kaiser*		
10:35	**Rapid Remyelination Leads to Vision Recovery After Pituitary Tumor Resection**	*G. Edward Vates*
10:50	**Efficacy and Safety of LCI699, A Potent 11β-hydroxylase Inhibitor, in Patients with Cushing's Disease: A 22-week, Multicenter, Open-label Study**	*Rosario Pivonello*
11:05	**Human Folliculostellate Cell Line PDFS Facilitates the Formation of Tumor-like Structures in Human Pituitary Tumor Primary Cultures**	*Xun Zhang*
11:20	**X-Linked Acro-Gigantism (X-LAG) Syndrome: A New Form of Infant-onset Pituitary Gigantism**	*Albert Beckers*
GENETICS *Co-Chairs: Marcello Bronstein and Ursula Kaiser*		
11:35	**AIP Mutations: Who Should We Screen?**	*Albert Beckers*
12:00 Noon	**PRESIDENTIAL ADDRESS, BUSINESS MEETING AND AWARDS LUNCHEON**	*Ariel Barkan*
1:00 PM Congress Adjourns		

Recent Updates in the Treatment of Acromegaly

March 4, 2015 at 1:00 PM

Hosted by Pfizer Endocrine Care

During this one-hour promotional program, an expert in endocrinology will review the diagnosis and management of acromegaly. To be discussed are the role of elevated IGF-1 levels in this condition, the efficacy and safety profile of a treatment option for acromegaly, and the implications of recent clinical practice guidelines for medication selection.

We gratefully acknowledge our corporate partners:

PLATINUM LEVEL SPONSOR:

NOVARTIS

UNRESTRICTED EDUCATIONAL GRANTS

GOLD LEVEL SUPPORTER:

IPSEN
Innovation for patient care

SILVER LEVEL SUPPORTERS:

novo nordisk®

Pfizer

EDUCATIONAL GRANT ALSO PROVIDED BY:

Corcept THERAPEUTICS

Please visit our Exhibitors in the Pavilion:

CORCEPT
CORTENDO
PFIZER
NOVARTIS

ABSTRACTS
INVITED LECTURES

OPENING PLENARY SESSION

Co-Chairs: Ariel Barkan and Mark Molitch

Prolactin Receptor Mutations

Rajesh Thakker

R V Thakker[1], C M Gorvin[1], P J Newey[1,2]

[1]University of Oxford, Radcliffe Department of Clinical Medicine, OCDEM, Churchill Hospital, Headington, Oxford, UK,
[2]University of Dundee, Division of Cardiovascular & Diabetes Medicine, Ninewells Hospital & Medical School, Dundee, UK

The prolactin receptor (PRLR) is a 598 amino-acid protein, that is a member of the class I cytokine receptor family, and is characterised by a 210 amino-acid extracellular domain (ECD), a single 25 amino-acid transmembrane domain (TMD), and a 363 amino-acid intracellular domain (ICD). The PRLR functions as a homodimer, and signals predominantly through the JAK2-STAT5 pathway, following binding by its ligand, prolactin. PRLR is expressed widely at multiple sites that include pituitary lactotrophs, mammary epithelial cells, adipocytes, and pancreatic beta cells. The physiological roles of PRLR in these cells may involve fertility, lactation, and metabolic regulation. In addition, the role of PRLR and its mutations in the aetiology of breast cancer and hyperprolactinaemia has been reported[1-5]. Thus, breast cancer has been reported to be associated with PRLR non-coding region polymorphisms[1,2], and 15% of women with multiple breast fibroadenomas have been reported to have two coding region variants (I76V and I146L), which result in a PRLR gain-of-function[3,4]. However, loss-of-function PRLR mutation (H188R) has been reported in three sisters who had hyperprolactinaemia that was not associated with pituitary tumours[5], consistent with the finding of hyperprolactinaemia in Prlr null mice (Prlr-/-), although pituitary hyperplasia and tumours were observed to occur in Prlr-/- females in late adulthood6. These findings indicate that PRLR variants/mutations that alter receptor function may have roles in diseases involving organs that express PRLRs, and that further studies are required to reveal these. As a step towards investigating this, we embarked on identifying additional PRLR variants, by analysing data from recent large-scale DNA sequencing projects, and selected non-synonymous, germline PRLR rare variants, defined as occurring in less than 1 in 500 individuals (mean allele frequency (MAF) <0.001), for investigation of their in vitro effects. Forty-eight non-synonymous germline PRLR rare variants were identified and 11 of these were selected for in vitro analysis as they were located near functional domains[7]. The 3 PRLR variants (I76V, I146L and H188R) reported in patients with breast tumours or hypoprolactinaemia were also similarly studied. Thus, 14 PRLR variants were investigated and these comprised 5 PRLR variants (G57S, I76V, I146L, E155K, and H188R) located in the extracellular domain (ECD) and 9 PRLR variants (F255S, G263D, D320Y, R327Q, E376Q, R453G, N492I, V535M, and E554Q) located in the intracellular domain (ICD). These PRLR variants were evaluated for effects on STAT5 signalling in HEK293 cells treated with prolactin (ranging from 0-1000ng/mL). STAT5 signalling was assessed by a phospho-STAT5 (pSTAT5) assay (AlphaScreen) that examined immediate signalling events, and a STAT5-dependent gene expression assay utilising a cytokine-inducible Src homology-2 domain containing protein (CISH) luciferase reporter, that examined later signalling events [7]. Nine PRLR variants had effects on STAT5 signalling[7], as follows. The PRLR variants E327Q and V535M, both located in the ICD, had increased pSTAT5 and CISH reporter activity, and the I146L variant (in the ECD) had only increased pSTAT5, consistent with PRLR gain-of-function. The variants H188R (in the ECD) and F255S (in the ICD) had reduction in pSTAT5 and CISH reporter activity, consistent with PRLR loss-of-function. However, the E155K (in ECD) and G263D (in ICD) had reduced pSTAT5 but normal CISH reporter activity, whilst the G57S (located in ECD) and E554Q (located in ICD) had normal pSTAT5 but reduced CISH reporter activity. Thus, PRLR variants may affect different aspects of receptor signalling and cause varying alterations of phenotypes, which are not currently reported in the DNA sequence databases[8]. The remaining five PRLR variants – I76V, D320Y, E376Q, R453G and N492I – had no effect on STAT5 signalling. In summary, our studies give further insights into PRLR structure-function and highlight that PRLR variants may be associated with in vitro alterations in receptor signalling, whose in vivo significance remains to be determined by assessment of phenotypic data from patients.

REFERENCES

1. Vaclavicek A, Hemminki K, Bartram CR, Wagner K, Wappenschmidt B, Meindl A, Schmutzler RK, Klaes R, Untch M, Burwinkel B, Försti A (2006). Association of prolactin and its receptor gene regions with familial breast cancer. *J Clin Endocrinol Metab*, 91:1513-9

2. Nyante SJ, Faupel-Badger JM, Sherman ME, Pfeiffer RM, Gaudet MM, Falk RT, Andaya AA, Lissowska J, Brinton LA, Peplonska B, Vonderhaar BK, Chanock S, Garcia-Closas M, Figueroa JD (2011). Genetic variation in PRL and PRLR, and relationships with serum prolactin levels and breast cancer risk: results from a population-based case-control study in Poland. *Breast Cancer Res,* 13: R42.

3. Bogorad RL1, Courtillot C, Mestayer C, Bernichtein S, Harutyunyan L, Jomain JB, Bachelot A, Kuttenn F, Kelly PA, Goffin V, Touraine P; Benign Breast Diseases Study Group (2008). Identification of a gain-of-function mutation of the prolactin receptor in women with benign breast tumors. *Proc Natl Acad Sci USA,* 105:14533-8.

4. Courtillot C1, Chakhtoura Z, Bogorad R, Genestie C, Bernichtein S, Badachi Y, Janaud G, Akakpo JP, Bachelot A, Kuttenn F, Goffin V, Touraine P; Benign Breast Diseases Study Group (2010). Characterization of two constitutively active prolactin receptor variants in a cohort of 95 women with multiple breast fibroadenomas. *J Clin Endocrinol Metab*, 95: 271-279.

5. Newey PJ1, Gorvin CM, Cleland SJ, Willberg CB, Bridge M, Azharuddin M, Drummond RS, van der Merwe PA, Klenerman P, Bountra C, Thakker RV (2012). Mutant prolactin receptor and familial hyperprolactinemia. *N Engl J Med*, 369: 2012-2020.

6. Schuff KG1, Hentges ST, Kelly MA, Binart N, Kelly PA, Iuvone PM, Asa SL, Low MJ (2002). Lack of prolactin receptor signaling in mice results in lactotroph proliferation and prolactinomas by dopamine-dependent and -independent mechanisms. *J Clin Invest,* 110: 973-981.

7. Gorvin C, Newey PJ, Thakker RV (2014). Functional Evaluation of Rare Genetic Variants in the Prolactin Receptor. ENDO 2014 OR-35-1.

8. Newey PJ, Thakker RV (2015). Frequency and spectrum of rare germline coding variants in hereditary endocrine disease genes: implications for clinical genetic studies. ENDO 2015 PP02-4.

Rajesh Thakker receives research income from Glaxo-SmithKline, Novartis, and NPS Pharmaceuticals; is Chairman of AstraZeneca Stratified Medicine Panel, and is a speaker/consultant for Novartis, Lilly, AstraZeneca, and Ipsen.

GH as a Metabolic Hormone

Rhonda Kineman

Jose Cordoba-Chacon, Manuel D. Gahete*, Raul M. Luque*, Rhonda D. Kineman

Department of Medicine, Section of Endocrinology, Diabetes and Metabolism, University of Illinois at Chicago and Research and Development Division of the Jesse Brown VA Medical Center, Chicago IL, USA

The true importance of endogenous GH in controlling adult metabolism, remains to be clarified since the bulk of our knowledge is based on studies of 1) short-term GH administration in normal subjects, 2) congenital GH deficiency (GHD), that might not reflect the consequences of GH decline after sexual maturation and 3) adult-onset, GHD (AOGHD) which is frequently accompanied by other pituitary defects, making it difficult to determine what changes are due specifically to GH loss. To circumvent these problems and more accurately define the importance of endogenous GH in adults, we developed a mouse model of adult-onset, isolated GHD (AOiGHD). AOiGHD mice exhibit an increase in fat/lean mass, post-prandial hypertriglyceridemia, reduced insulin-dependent suppression of hepatic glucose production and age-dependent impairment in β-cell function, despite improved systemic insulin sensitivity. Based on these observations, we hypothesize that impaired hepatic function is key to the development of metabolic disease in the AOGHD patients. In order to specifically study the role of the liver in mediating the metabolic effect of GH, we recently generated a mouse model with adult-onset hepatic GH resistance (aLivGHRkd). Just seven days after loss of the GHR in the adult liver there is an increase in hepatic de novo lipogenesis (DNL) associated with hepatosteatosis, hypertriglyceridemia and hepatic insulin resistance, without changes in systemic insulin sensitivity, glucose tolerance or adipose tissue lipolysis. Taken together, our data demonstrate that the maintenance of hepatic GH signaling is critical to maintain appropriate hepatic insulin signaling and to control DNL. These actions of GH on liver function may not only be relevant to patients with acquired GHD, but may also be important in understanding the progression of non-alcoholic fatty liver disease (NAFLD) in the general population, since GH and IGF-I levels are reduced and hepatic DNL is increased in patients with NAFLD.

**current academic affiliation, Department of Cell Biology, Physiology and Immunology, University of Cordoba, Cordoba Spain 14014*

Rhonda Kineman has no relationships to disclose.

ACROMEGALY

Chair: Nienke Biermasz

Oral Ocreotide Therapy of Acromegaly

Vera Popovic

Endocrinology Clinic, Clinical Ceneter, University Belgrade, Belgrade, Serbia

Background: A novel oral octreotide formulation was tested for efficacy and safety in a phase III multicenter open-label dose-titration baseline-controlled study for acromegaly.

Methods: We enrolled 155 complete or partially controlled patients [IGF-I <1.3 upper limit of normal (ULN), and 2-hr integrated growth hormone (GH) <2.5ng/mL] while receiving injectable somatostatin receptor ligand (SRL) for ≥3 months. Subjects were switched to 40 mg /day oral octreotide capsules (OOC), dose escalated to 60, and up to 80 mg/day, to control IGF-I. Subsequent fixed-doses were maintained for 7 month core treatment, followed by voluntary 6 month extension.

Results: Of 151 evaluable subjects initiating OOC, 65% maintained response and achieved the primary endpoint of IGF-I <1.3 ULN and mean integrated GH <2.5ng/mL at the end of the core treatment period and 62% at the end of treatment (up to 13 months). The effect was durable and 85 % of subjects initially controlled on OOC, maintained this response up to 13 months. Baseline responses to injectable SRLs, predicted response to octreotide capsules.

When controlled on OOC, GH levels were reduced compared to Baseline and acromegaly-related symptoms improved. Of 102 subjects completing core treatment, 86% elected to enroll into 6-month extension. Octreotide capsules were safe and well tolerated, majority of AEs were transient and consistent with known safety profile for SRLs, with no Injection site reactions.

Conclusions: OOC, an oral therapeutic peptide achieves efficacy in controlling IGF-I and GH following switch from injectable SRLs, for up to 13 months, with a safety profile consistent with approved SRLs. OOC appears to be effective and safe as acromegaly monotherapy.

Vera Popovic has no relationships to disclose.

Acromegaly Effects on Bone Metabolism and the Musculoskeletal System

K.M.J.A. Claessen

Medisch Centrum Haaglanden Westeinde, The Hague, The Netherlands

Acromegaly patients suffer from a high prevalence of late manifestations of transient GH excess, despite achievement of biochemical disease control. In this respect, especially skeletal complications significantly impair quality of life (QoL). Arthropathy is one of the most common complications with a prevalence that is 4 to 12 times increased compared to healthy controls. Although acromegalic arthropathy shares features with primary osteoarthritis (OA), radiographic features significantly differ. In acromegalics, predominantly osteophytosis is seen in combination with preserved joint spaces, indicating cartilage hypertrophy. A recent study shows that joint cartilage is not only thickened in acromegalics, but is also of altered quality with increased water content compared to primary OA subjects. Furthermore, there is evidence for clinical and radiographic OA progression in a large subset of patients in remission. Remarkably, largest OA progression is seen in patients controlled by SMS analogs, which may indicate the need of more stringent disease control.

Next to arthropathy, acromegaly patients suffer from a high prevalence (60%) of vertebral fractures, despite remission of GH excess. Highest prevalence of vertebral fractures is documented in men and in patients with hypogonadism. Vertebral fractures occur in the presence of normal bone mineral density (BMD), suggesting that abnormalities in bone quality may explain the high vertebral fracture risk in these patients. Furthermore, it was recently shown in several studies that in 20% of patients vertebral fractures progress despite achievement of biochemical remission.

In this lecture, an oversight of the skeletal manifestations of acromegaly is given with its underlying pathophysiology, diagnostic tools, clinical picture, disease course and therapeutic consequences.

K.M.J.A. Claessen has no relationships to disclose.

What Can We Learn by Measuring Circulating GH Rhythms in Acromegaly?

Antônio Ribeiro-Oliveira Jr.

Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

Growth hormone (GH), like all other pituitary hormones, is secreted in a pulsatile manner. The secretory pattern of GH is characterized by 2 kinds of rhythmicity: a periodic nyctohemeral component and an episodic pulsatile component. The former is represented by a remarkable augmentation of GH secretion after the onset of sleep, in close association with slow wave sleep. The later is manifest as rapid secretory discharges occurring in a seemingly random fashion during waking hours and coalescing into apparent pulses. A complex interplay involving mainly GHRH and somatostatin, but also influenced by other physiological regulators such as nutrients and steroids, are involved in this rhythm physiology. This GH secretion in humans is sexually dimorphic. In men, GH profiles have lower baseline GH concentrations, are almost apulsatile during the waking hours but exhibit prominent nocturnal augmentation with the onset of slow wave sleep. In contrast, women have higher interpulse GH levels, obvious GH pulsatility during the daytime and a relatively blunted nocturnal GH pulse. Nevertheless, a complex three wave dominant rhythm pattern is present in both men and women. Interestingly, although this pattern is kept in the elderly, there is an age-decline of GH secretion.

Traditionally, acromegaly is viewed as a disease resulting from GH hypersecretion from a complete autonomous pituitary somatotropinoma. However, this paradigm may be contested if a hypothalamic regulation is shown to be present in acromegaly. The analysis of acromegaly GH profiles have shown that these patients clearly show the appearance of the nocturnal GH "waves", implying that the hallmark of growth hormone secretion architecture is preserved. Furthermore, the complex three wave rhythmicity pattern can be well documented, similarly to controls. In addition, this secretion maintains the sexual dimorphism in these patients. Interestingly, the age-decline in GH secretion can also be observed in acromegaly. All together, these data demonstrate that GH secretion from pituitary somatotropinomas is not entirely autonomous but still subject to the normal hypothalamic regulation, potentially at a different set point and similarly to what is known for Cushing's disease.

What else is GH rhythms worth for? First, there is a considerable overlap between 24-h GH profiles of acromegalic patients and normal individuals, especially for those with mild biochemical acromegaly. Interestingly, these patients may be also easily glucose suppressible and contribute to the endless debate on the best GH nadir cut-off in acromegaly. Second, plasma IGF-1 concentrations in acromegaly correlate well with mean 24-h GH means. However, this correlation has been shown to be related to the nadir GH, and not otherwise related to pulse peaks. Third, the total GH outputs, rather than the pulses, seem to be responsible for worsening of glucose tolerance. The pulses, however, increase adipose tissue lipolysis, which may indirectly impact glucose tolerance. Fourth, the analysis of both acromegaly and normal profiles suggest that neither a single GH value nor an abbreviated sampling are sufficient to proclaim a safe GH level in an individual patient.

Antônio Ribeiro-Oliveira Jr has no relationships to disclose.

Evidence Based Guidelines in Acromegaly: Limitations and Utility

Mônica Gadelha

Neuroendocrine Research Center, Endocrinology Unit, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Evidence-based guidelines in acromegaly are developed combining the best available scientific substantiation in the literature and experts' opinion. They have been indeed very helpful in the decision-making processes in medical practice.

Very recently, the Endocrine Society clinical practice guideline for acromegaly was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to characterize the strength of recommendations and the quality of evidence. The European Society of Endocrinology cosponsors the guideline. Important issues regarding diagnosis and treatment, even in special circumstances (e. g. pregnancy), are very well addressed in the guideline. An algorithm for integrated multidisciplinary therapeutic approach is proposed to guide physicians, mainly neuroendocrinologists, in the management of patients with acromegaly, what should be done in referral centers.

The utility of evidence-based guidelines seems to be obvious. However, relevant limitations should be considered and will be discussed during this debate.

Mônica Gadelha is a speaker and advisory board member for Novartis, is a speaker for Ipsen, is a PI in clinical trials for Novartis and Ipsen, and is an Investigator for Novartis and Pfizer.

Evidence Based Guidelines in Acromegaly: Limitations and Utility

Peter J Trainer

The Christie NHS Foundation Trust, Wilmslow Road, Manchester, UK

The utility of guidelines comes from their ability to assist physicians in delivering 'best-practice' to their patients, which is particularly important when dealing with rare diseases when the experience of many clinicians will be limited. Since 1999, the Pituitary Society has held nine acromegaly consensus meetings, with the tenth scheduled for later this year, resulting in ten publications to date. The major and very real achievement of these meetings has been the creation and adoption internationally of biochemically-defined goals of acromegaly treatment. Evidence-based guidelines have resulted in a consistent standard against which to judge the outcomes of clinical trials, relieving investigators of the need, or flexibility, to define their own end-points. Application of these stringent targets has resulted in recognition that some agents may not be as effective as initially believed, with the consequence that physicians and patients can be more realistic with their expectations when commencing treatment and are better able to recognise the need for additional therapy. Development of internationally recognised biochemical criteria for successful treatment has focussed attention on assay performance and the multitude of factors influencing the applicability of consensus guidelines to local practice. Bias in GH and IGF-I assays, varied reference materials, the nonsense of geographical variation in reporting units and conversion factors have all come under scrutiny as part of the iterative process of evidence-based guideline development.

Dr Gadelha is a fine endocrinologist and orator who doubtlessly will make a persuasive argument for the futility of evidence-based consensus guidelines, or at least highlight their limitations, but judge her not by her words but rather by her actions. She is a very busy woman with a full diary to whom time is precious. However did she find the time to attend the last Pituitary Society consensus meeting in 2013? Will she be attending the next consensus meeting in Madrid? If she did, if she will - Vote Yes!

Peter Trainer receives travel and research support from Antisense. His presentation will include discussion of product(s) unlabeled (off-label) for use as approved by the FDA or by the equivalent regulatory authority in the country in which the studies or trials were performed.

GROWTH HORMONE – JOINT GRS SESSION

Chair: John Kopchick

GH Regulation of Electrolyte Balance

Peter Kamenický

Paris-Sud University, Le Kremlin-Bicetre, France, Department of Endocrinology and Reproductive Medicine, Bicetre Hospital, France

This talk focuses on the GH regulation of the electrolyte balance, taking into account major advances in renal physiology and growth hormone biology, allowing us to move our understanding of tubular transports from a cellular to a molecular level. GH and IGF-I are involved in hormonal fine-tuning of tubular handling of sodium, water, calcium and phosphate. The impact of GH and IGF-I on these tubular functions becomes clearly apparent in pathophysiological situations of GH hypersecretion and deficiency. One of the best-established effects of GH and IGF-I excess on the kidney is their sodium-retaining action in the distal tubule, linked to enhanced Epithelial Sodium Channel (ENaC)-dependent sodium transport. This tubular action is responsible for extracellular volume expansion, contributing to soft tissue swelling and arterial hypertension in acromegalic patients. Changes in phospho-calcium metabolism in acromegaly and the reciprocal changes in GH deficiency may be associated with increased skeletal fragility observed in these diseases. Detailed information on this topic may be found in our recent review (Kamenický et al., Endocrine Reviews, 2014).

Peter Kamenický has no relationships to disclose.

GH-Induced Signaling in Human Muscle

Jens Otto Jørgensen

Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

The intracellular GH signaling pathways have been extensively studied mainly in rodent liver models in vitro. The JAK-STAT pathway and ensuing transcription of target genes such as SOCS/CISH and IGF-I are of recognized importance in addition to alternative pathways such as MAPK, and Akt/PKB. The metabolic effects of GH may however differ between species and GH signaling may differ between in vitro and in vivo. We therefore have studied stimulated GH signaling in human skeletal in vivo in a number of experiments for almost 10 years. We consistently record GH-induced phosphorylation of STAT5 in skeletal muscle peaking after 30 min and lasting for 120 min. This mainly associates with transcription of SOCS/CISH genes after 60 – 120 min of which CISH is most pronounced; IGF-I gene transcription is also induced albeit with less consistency. In contrast to rodent data we do not find evidence of GH-induced activation of alternative pathways such as MAPK or AKt/PKB in human muscle in vivo. Using a gene array we identified 79 genes responsive to acute GH exposure in human skeletal muscle in vivo (0.7- or 1.4-fold changes in expression). The coded proteins functioned in cellular development and growth, and gene expression. Next to CISH, the most upregulated gene was ANGPTL4 and the protein is involved in fatty acid metabolism. In addition to studying the response to exogenous GH we have also documented activation of in vivo GH signaling in human muscle in response to fasting, exercise and ghrelin infusion. More recently we compared stimulated GH signaling in the context of administration of somatostatin and its analogues (SA) in both healthy subjects and patients with acromegaly and find evidence to indicate that SA may exert (peripheral) effects to mitigate the insulin antagonistic effects of GH. In conclusion, we consider our human in vivo model a valuable supplement to in vitro and animal models.

Jens Otto Jørgensen has no relationships to disclose.

rhGH by Athletes: Is the Evidence Valid?

Richard Holt

Human Development and Health Academic Unit, Faculty of Medicine, University of Southampton, Southampton, UK

Anecdotal evidence suggests that growth hormone (GH) has been widely misused by athletes since the early 1980s because of its anabolic and lipolytic properties, at least a decade before it was used therapeutically by adult endocrinologists. There is debate about whether GH is ergogenic and most scientific studies have not shown a performance enhancing effect. This presentation will address why there is this discrepancy of opinion between athletes and scientists and why the presenter believes that the scientists are wrong.

Although GH is on the World Anti-Doping Agency list of banned substances, the detection of misuse with GH is challenging. Two complementary approaches have been developed to detect GH misuse. The first is based on the measurement of pituitary GH isoforms and was introduced at the Athens Olympic Games. The second is based on the measurement of insulin like growth factor-I (IGF-I) and amino-terminal pro-peptide of type III collagen (P III NP), two markers of GH action. Six weeks after its introduction at the London Olympic Games, two power lifters were disqualified after admitting to taking GH after adverse analytical findings from the test. The second part of this presentation will address the advantages and disadvantages of the two methods, with a focus on their scientific validity.

Richard Holt has no relationships to disclose.

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

Differential Effects of GH on White Adipose Tissue

Darlene Berryman

School of Allied Health Sciences and Wellness, College of Health Sciences and Professions, and Department of Biomedical Sciences, Heritage College of Osteopathic Medicine, Ohio University, Athens, OH, USA

Adipose tissue was once thought to primarily function as an energy reservoir. However, more recent evidence demonstrates that adipose tissue is significantly more intricate and dynamic than previously appreciated. GH, a pleotropic hormone acting on numerous organs and cell types in the body, has a strong influence on adipose tissue function and complexity. Among these complexities are the unique physiological and pathophysiological functions of different depots of adipose tissue. In this presentation, I will describe data from mouse lines with increased, decreased, and absence of GH action and the resultant impact on white adipose tissue. Interestingly, these mouse lines demonstrate adiposity profiles that are counterintuitive to health and longevity. That is, mice with excess GH action are lean but insulin resistant and short-lived (or "unhealthy lean"). On the other hand, mice with no GH action are obese but are insulin sensitive and long lived (or "healthy obesity"). Thus, these extremes in GH action provide a fascinating model system to not only study how GH alters white adipose tissue but also how features of adipose tissue, besides simply mass, are responsible for metabolic dysfunction. One trend that has emerged from these studies is that the impact of GH on adipose tissue is depot-, sex- and age-dependent, which requires one to consider these variables when designing studies or in interpretation of findings. Further, while GH alters the pre-adipocyte and adipocyte directly, the impact on adipose tissue extends beyond these cell types. That is, intrinsic adipose tissue differences exist in the level of fibrosis, angiogenesis, and immune cell infiltration in response to altered GH levels, revealing the importance of the non-adipocyte fraction of cells in response to GH. The influence of GH on these other cell types is likely important for the overall health of the tissue.

Darlene Berryman has no relationships to disclose.

MEET THE PROFESSOR CONCURRENT WORKSHOPS

Aggressive Pituitary Tumors or Localized Pituitary Carcinomas

Luis V. Syro

[1]**Luis V. Syro,** [2]**Fabio Rotondo,** [3]**Michael D. Cusimano,** [2]**Kalman Kovacs**

[1]Department of Neurosurgery, Hospital Pablo Tobon Uribe and Clinica Medellín, Medellín, Colombia; [2]Department of Laboratory, Division of Pathology, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; [3]Department of Surgery, Division of Neurosurgery, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada

Pituitary tumors arise in or differentiate into adenohypophysial cells. They can produce GH, PRL, ACTH, TSH, FSH, LH and/or alpha subunit, or may be silent, unassociated with hormone release and symptoms indicating hormonal hyperfunction. According to the World Health Organization (WHO) they may be classified as typical adenomas, atypical adenomas and carcinomas. The majority of pituitary tumors are slowly growing, well demarcated, non-invasive adenomas showing no major cellular and nuclear pleomorphism, few mitotic figures and a Ki-67 nuclear index less than 3%. Pituitary carcinomas can only be diagnosed if cerebrospinal and/or systemic metastases can be documented. Using these classification criteria, they are rare, less than 1% of pituitary tumors. Pituitary carcinomas secrete most frequently PRL or ACTH; however, they may produce the remaining adenohypophysial hormones or may not release hormones that would normally cause clinical endocrine symptoms. They may develop by transformation from adenomas or may arise de novo from nontumorous adenohypophysial cells.

The WHO classification of typical and atypical adenomas does not correlate with tumor clinical behavior. Usually tumors that exhibit high rate of recurrence and resistance to conventional treatments are considered aggressive adenomas and they seem to represent a distinct entity. Extensive work was carried out in many laboratories and a large number of biomarkers were investigated. Several genetic and epigenetic alterations were found, but no conclusive criterion is available to diagnose definitively aggressive adenomas. It would be of pivotal importance to reveal how frequent these tumors are and to find specific morphologic, genetic-epigenetic markers which make possible their correct diagnosis.

The aim of future research is defining aggressiveness, in terms of morphologic, molecular-genetic and radiological markers, as well as histopathological criteria. Some of them have malignant potential and their recognition is of crucial importance. It is a real possibility that some of the tumors diagnosed as aggressive adenomas underwent the "malignant switch" and are carcinomas without recognized metastases. Their identification would be of practical significance because it would reveal prognosis and treatment options.

Luis V. Syro has no relationships to disclose.

Determination of Remission after Surgery for Cushing's Disease

Michael Buchfelder

Department of Neurosurgery, University of Erlangen Nurnberg, Erlangen, Germany

Brooke Swearingen

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

The reliable determination of remission after surgery for Cushing's disease has proven difficult. There are multiple different criteria described in the literature. Criteria of varying stringency have been proposed, obtained at various post-operative time points, with and without steroid replacement, and there is variable correlation with the risk of recurrence. We will review the post-operative management of these patients, including remission criteria, steroid replacement, and imaging.

Michael Buchfelder has no relationships to disclose.

Brooke Swearingen has no relationships to disclose.

How Do I Interpret GH and IGF1 Assays?

Martin Bidlingmaier

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

Martin Bidlingmaier receives consulting fees from Diasorin, IDS, and OPKO.

Pituitary Disorders in Pregnancy

Züleyha Karaca

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

The pituitary gland is altered by both anatomical and physiological changes during pregnancy. The most prominent finding is the physiological enlargement of the pituitary gland due to lactotroph hyperplasia. Pituitary and target hormone levels show some differences from non-pregnant state due to changing needs of mother and fetus throughout gestation, and placental hormone production (Table 1).

Pituitary adenomas may grow during pregnancy besides adversely affecting fetus and mother by hormone secretion. The risk of tumor growth during gestation is not high for pituitary adenomas. Prolactinomas are the most common pituitary adenomas encountered during pregnancy since the disease is common among women of reproductive age and fertility can be easily restored after medical treatment. Acromegaly is the second most common functional pituitary adenoma seen in relation to gestation after prolactinomas. It is safe to discontinue medical treatment after confirmation of pregnancy in both GH and PRL secreting pituitary adenomas. Approach to the patients with prolactinoma and acromegaly are summarized in Figure 1 and 2. Cushing's disease is rare during gestation and usually requires treatment since hypercortisolemia adversely affects pregnancy.

Spontaneous pregnancy is rare in patients with hypopituitarism due to altered gonadotroph functions. Evaluation of pituitary functions and treatment of hypopituitarism requires special attention during gestation. Important keypoints regarding treatment of hypopituitarism are summarized in Figure 3.

Table 1: Physiological hormonal changes during pregnancy

Pituitary hormones	Releasing and inhibitory hormones	Target hormones	Binding proteins
Pituitary ACTH ↑ Placental ACTH ↑	Stim: -Hypothalamic CRH -Placental CRH	-Free and bound cortisol↑ -Urinary cortisol metabolites↑	CBG↑ CRH-BG↑
Pituitary GH ↓ Placental GH-V↑	Stim: -Hypothalamic GHRH -Placental GHRH Inh: -placental GH-V	-IGF-1 slightly↑ -IGF-1 also produced from placenta	GH-binding protein↑
Pituitary PRL ↑ Decidual PRL ↑	Inh: -Hypothalamic dopamine		
FSH, LH↓	Stim: -GnRH (decreased response) Inh: -placental sex steroids	Estrogen↑ Progesterone↑	SHBG↑
TSH↓ in the 1st trimester	Stim: -Hypothalamic TRH Inh: -Placental HCG	-Free T4 ↑ in the 1st trimester and slightly ↓ in the 2nd half of pregnancy -Total T4 ↑	TBG↑

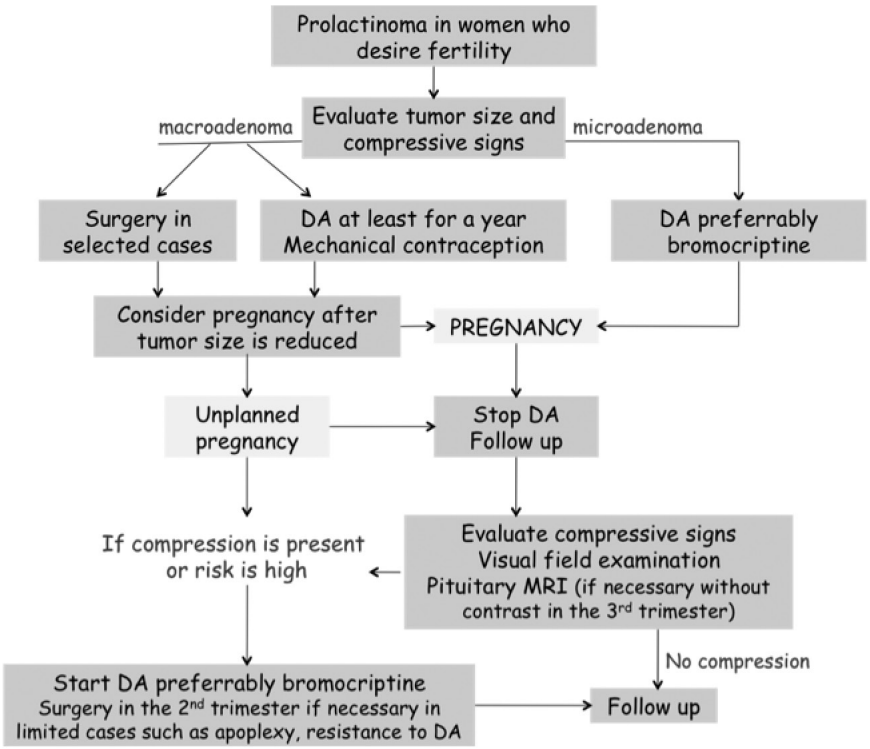


Figure 1: Management of prolactinoma associated with pregnancy DA: dopamine agonist

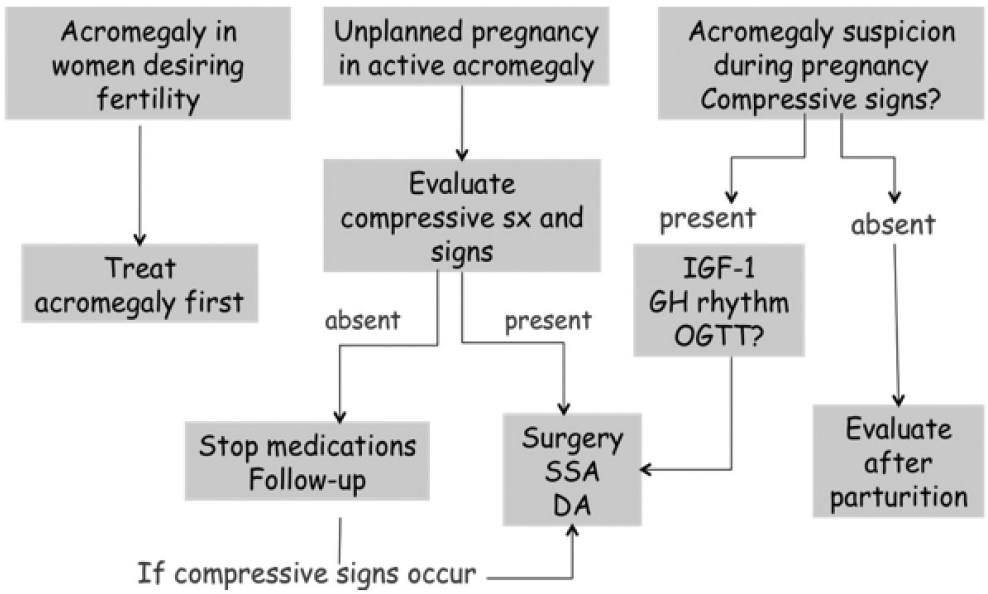


Figure 2: Management of acromegaly associated with pregnancy. DA: dopamine agonist, SSA: somatostatin analogs

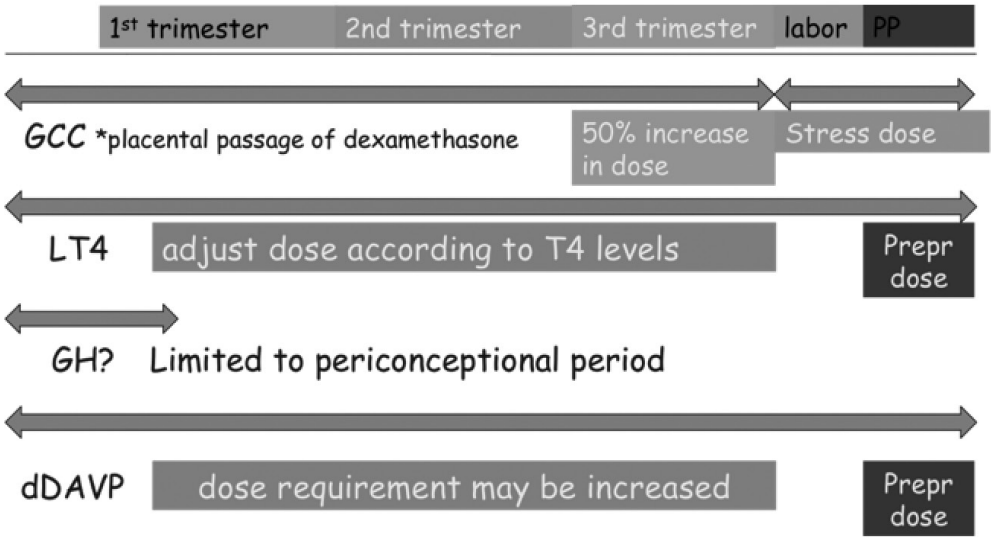


Figure 3: Keypoints of treatment of hypopituitarism during gestation

PP: postpartum, GCC: glucocorticoid, LT4: levothyroxine, prepr: prepregnancy, GH: growth hormone

Züleyha Karaca has no relationships to disclose.

Cyclic Cushing's Syndrome

Nicholas Tritos

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

Case definition and clinical significance

Cyclic Cushing's syndrome (CS) is characterized by spontaneous episodes of intermittent, recurrent hypercortisolism that cannot be explained as a consequence of medical intervention. There is no universally agreed upon case definition. One proposed definition requires the presence (at a minimum) of three secretory peaks (episodes characterized by cortisol excess) with two intervening "valleys" (periods during which cortisol secretion is normal or even low) (1). Other investigators have proposed the presence of a single (at a minimum) secretory cycle, characterized by two peaks and one trough, as meeting the case definition of cyclic CS (2). The secretory cycles can be either regular (periodic) or irregular. Patients may have either persistent or intermittent symptoms, coinciding with episodes of cortisol excess.

The diagnosis of cyclic CS can be challenging, since these patients may present with symptoms and signs consistent with the presence of hypercortisolism and either normal or erratic results on initial diagnostic testing (including 24 hour urine free cortisol, late-night salivary cortisol or dexamethasone suppression testing). In the presence of clinical suspicion of CS, perseverance is needed in order to avoid missing the diagnosis of cyclic CS. Furthermore, the presence of cyclic CS may hamper the assessment of outcomes of surgery or other medical intervention.

Learning objectives

1. Discuss the case definition, epidemiology and presentation of patients with cyclic CS.

2. Review the diagnostic evaluation of patients with suspected cyclic CS.

3. Describe the management of patients with cyclic CS (with emphasis on pituitary cause).

Epidemiology

There are only retrospectively collected data on the epidemiology of cyclic CS, which was initially described in case reports and small case series and considered to be rare (3-8). More recently, retrospective analyses have suggested that cyclic Cushing's disease (CD) may occur in approximately 15-19% of all patients with CD (2, 9, 10). In another study, cyclic CS was present in 36% of all patients with CS (11). Prospectively collected data would be welcome in order to further characterize both the epidemiology and natural history of this condition.

Causes and pathophysiology

The presence of cyclic CS has been described in patients with pituitary adenomas, ectopic ACTH secreting neoplasms or adrenal tumors. In a review of 65 published cases, there were 35 (54%) patients with pituitary tumors, 17 (26%) with ectopic ACTH secreting tumors, 7 (11%) with adrenal lesions and 6 (9%) patients with CS of unclear etiology (1). The focus of the present manuscript and session is cyclic CS of pituitary origin (cyclic CD).

The pathophysiology of this condition remains poorly understood. Proposed mechanisms include the occurrence of episodic adenoma cell growth or death, Intratumoral hemorrhage, the presence of fluctuations in negative feedback mechanisms involved in ACTH secretion by corticotroph adenomas or fluctuations in CRH secretion as a result of variations in activity of neuronal (dopaminergic, GABAergic or serotoninergic) pathways (12-19).

Presentation and Diagnosis

Cyclic CS has been reported in patients of both genders across the lifespan (1, 20-23). Some patients experience intermittent symptoms coinciding with episodes of cortisol excess, interspersed with clinical remission (or rarely intervening episodes of hypoadrenalism). Other patients experience less obvious fluctuations in symptoms and signs.

As is the case in other patients with CS, the diagnostic process begins with a careful history and physical examination. The possibility of exogenous glucocorticoid administration leading to manifestations of hypercortisolism should always be considered. Other diagnostic considerations include "pseudo-Cushing's states" (depression, alcohol excess, and others) (24).

Laboratory tests in patients with cyclic CS (including 24 hour urine free cortisol, late night salivary cortisol and dexamethasone suppression tests) are anticipated to yield variable results, consistent with the presence of intermittent hypercortisolism; paradoxical cortisol responses to dexamethasone administration have also been described (1, 2, 25). As a corollary, it may often be necessary to pursue the diagnosis of cyclic CS despite normal results on initial testing, if clinical suspicion for this condition persists. Selection of laboratory tests that are least cumbersome for the patient to complete is helpful in these cases, which often require extensive and frequent testing. Tests proposed for this purpose include morning urine cortisol to creatinine ratio, five point serum cortisol curve, and an assay of cortisol levels in hair specimens (currently investigational) (2, 26-28). In our practice, we have used late night (11 pm) salivary cortisol, repeated nightly for days to weeks, as a convenient means of evaluating the possibility of cyclic CS (29-32).

Once the diagnosis of hypercortisolism is confirmed, morning plasma ACTH levels are generally helpful in distinguishing between ACTH-dependent and ACTH-independent causes (33). Pituitary imaging using MRI is advisable in patients with ACTH-dependent CS. In the absence of a clear cut sellar mass (> 5-10 mm in diameter), bilateral inferior petrosal sinus sampling is recommended in order to distinguish between a central and an ectopic source of ACTH excess. In patients with suspected cyclic CS, it is critical to perform any endocrine tests aiming at establishing the source of CS only during episodes of cortisol excess (13, 33).

Management

Once the cause of cyclic CS is established, patients should be referred for resection of the underlying tumor (if possible). In patients with cyclic CD, referral to an experienced pituitary neurosurgeon is recommended, as is true of all patients with CD (or other pituitary tumors) (34, 35). In one retrospective study of patients with cyclic CD, a pituitary adenoma was less likely to be found at surgery and remission rates were lower in comparison with patients whose condition did not exhibit cyclic variations (2). Postoperatively, frequent monitoring of early morning serum cortisol, 24 hour urine free cortisol and late-night salivary cortisol levels is advisable in order to assess if remission has occurred. Our practice has been to place these patients on low-dose dexamethasone while postoperative testing is in progress. Biochemical remission of hypercortisolism in patients with cyclic CD can be difficult to establish with confidence, owing to the intermittent nature of cortisol excess, which might falsely suggest that remission is present if testing is carried out during a period of spontaneous quiescence of disease activity.

For patients with persistent or recurrent cyclic CD after transsphenoidal pituitary surgery, treatment options may include additional pituitary surgery, radiotherapy with interim medical therapy (including centrally acting agents, steroidogenesis inhibitors or glucocorticoid receptor antagonists) or bilateral adrenalectomy (33, 36). Patients on medical therapy require careful monitoring to detect the possible development of hypoadrenalism, which might result from the additive effects of the pharmacologic agent used and spontaneous fluctuations in cortisol excess. Careful and long-term follow up is needed to ascertain therapeutic outcomes in individual patients whose condition might spontaneously remit as a result of the cyclicity of hypercortisolism rather than a result of therapeutic interventions.

Outline of presentation

The session includes a case-based discussion of cyclic CD. The following questions will be discussed during the session:

- When should cyclic CD be suspected?
- What are the pitfalls in the diagnostic evaluation of patients with suspected cyclic CD?
- What are the challenges in the management of patients with cyclic CD?

REFERENCES

1. Meinardi JR, Wolffenbuttel BH, Dullaart RP 2007 Cyclic Cushing's syndrome: a clinical challenge. Eur J Endocrinol 157:245-254
2. Alexandraki KI, Kaltsas GA, Isidori AM, Akker SA, Drake WM, Chew SL, Monson JP, Besser GM, Grossman AB 2009 The prevalence and characteristic features of cyclicity and variability in Cushing's disease. Eur J Endocrinol 160:1011-1018
3. Bailey RE 1971 Periodic hormonogenesis--a new phenomenon. Periodicity in function of a hormone-producing tumor in man. The Journal of Clinical Endocrinology and Metabolism 32:317-327
4. Bassoe HH, Emberland R, Stoa KF 1958 Fluctuating steroid excretion in Cushing's syndrome. Acta Endocrinol (Copenh) 28:163-168
5. Bochner F, Burke CJ, Lloyd HM, Nurnberg BI 1979 Intermittent Cushing's disease. Am J Med 67:507-510
6. Green JR, van't Hoff W 1975 Cushing's syndrome with fluctuation due to adrenal adenoma. The Journal of Clinical Endocrinology and Metabolism 41:235-240
7. Liberman B, Wajchenberg BL, Tambascia MA, Mesquita CH 1976 Periodic remission in Cushing's disease with paradoxical dexamethasone response: an expression of periodic hormonogenesis. The Journal of clinical Endocrinology and Metabolism 43:913-918
8. Birke G, Diczfalusy E 1956 Fluctuation in the excretion of adrenocortical steroids in a case of Cushing's syndrome. The Journal of Clinical Endocrinology and Metabolism 16:286-290
9. McCance DR, Gordon DS, Fannin TF, Hadden DR, Kennedy L, Sheridan B, Atkinson AB 1993 Assessment of endocrine function after transsphenoidal surgery for Cushing's disease. Clin Endocrinol (Oxf) 38:79-86
10. Streeten DH, Anderson GH, Jr., Dalakos T, Joachimpillai AD 1997 Intermittent hypercortisolism: a disorder strikingly prevalent after hypophysial surgical procedures. Endocr Pract 3:123-129
11. Atkinson AB, Kennedy AL, Carson DJ, Hadden DR, Weaver JA, Sheridan B 1985 Five cases of cyclical Cushing's syndrome. Br Med J (Clin Res Ed) 291:1453-1457
12. Alarifi A, Alzahrani AS, Salam SA, Ahmed M, Kanaan I 2005 Repeated remissions of Cushing's disease due to recurrent infarctions of an ACTH-producing pituitary macroadenoma. Pituitary 8:81-87
13. Mantero F, Scaroni CM, Albiger NM 2004 Cyclic Cushing's syndrome: an overview. Pituitary 7:203-207

14. Schweikert HU, Fehm HL, Fahlbusch R, Martin R, Kolloch R, Higuchi M, Kruck F 1985 Cyclic Cushing's syndrome combined with cortisol suppressible, dexamethasone non-suppressible ACTH secretion: a new variant of Cushing's syndrome. Acta Endocrinol (Copenh) 110:289-295

15. Marko NF, Hamrahian AH, Hatipoglu B, Weil RJ 2013 Relapsing, remitting hypercortisolism in Cushing's disease due to intratumoral hemorrhages in pituitary microadenoma. Journal of Clinical Neuroscience : official journal of the Neurosurgical Society of Australasia 20:753-756

16. Beckers A, Stevenaert A, Pirens G, Flandroy P, Sulon J, Hennen G 1990 Cyclical Cushing's disease and its successful control under sodium valproate. J Endocrinol Invest 13:923-929

17. Estopinan V, Varela C, Riobo P, Dominguez JR, Sancho J 1987 Ectopic Cushing's syndrome with periodic hormonogenesis--a case suggesting a pathogenetic mechanism. Postgrad Med J 63:887-889

18. Hsu TH, Gann DS, Tsan KW, Russell RP 1981 Cyproheptadine in the control of Cushing's disease. Johns Hopkins Med J 149:77-83

19. Watanobe H, Aoki R, Takebe K, Nakazono M, Kudo M 1991 In vivo and in vitro studies in a patient with cyclical Cushing's disease showing some responsiveness to bromocriptine. Horm Res 36:227-234

20. Atkinson AB, Chestnutt A, Crothers E, Woods R, Weaver JA, Kennedy L, Sheridan B 1985 Cyclical Cushing's disease: two distinct rhythms in a patient with a basophil adenoma. The Journal of Clinical Endocrinology and Metabolism 60:328-332

21. Atkinson AB, Kennedy A, Wiggam MI, McCance DR, Sheridan B 2005 Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance. Clin Endocrinol (Oxf) 63:549-559

22. Atkinson AB, McCance DR, Kennedy L, Sheridan B 1992 Cyclical Cushing's syndrome first diagnosed after pituitary surgery: a trap for the unwary. Clin Endocrinol (Oxf) 36:297-299

23. Gunther DF, Bourdeau I, Matyakhina L, Cassarino D, Kleiner DE, Griffin K, Courkoutsakis N, Abu-Asab M, Tsokos M, Keil M, Carney JA, Stratakis CA 2004 Cyclical Cushing syndrome presenting in infancy: an early form of primary pigmented nodular adrenocortical disease, or a new entity? The Journal of Clinical Endocrinology and Metabolism 89:3173-3182

24. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM 2008 The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology and Metabolism 93:1526-1540

25. Krysiak R, Kedzia A, Okopien B 2012 Cyclic Cushing's syndrome. Acta Clinica Belgica 67:30-33

26. Manenschijn L, Koper JW, van den Akker EL, de Heide LJ, Geerdink EA, de Jong FH, Feelders RA, van Rossum EF 2012 A novel tool in the diagnosis and follow-up of (cyclic) Cushing's syndrome: measurement of long-term cortisol in scalp hair. The Journal of Clinical Endocrinology and Metabolism 97:E1836-1843

27. Mullan KR, Atkinson AB 2008 Endocrine clinical update: where are we in the therapeutic management of pituitary-dependent hypercortisolism? Clin Endocrinol (Oxf) 68:327-337

28. Mullan KR, Atkinson AB, Sheridan B 2007 Cyclical Cushing's syndrome: an update. Curr Opin Endocrinol Diabetes Obes 14:317-322

29. Hermus AR, Pieters GF, Borm GF, Verhofstad AA, Smals AG, Benraad TJ, Kloppenborg PW 1993 Unpredictable hypersecretion of cortisol in Cushing's disease: detection by daily salivary cortisol measurements. Acta Endocrinol (Copenh) 128:428-432

30. Mosnier-Pudar H, Thomopoulos P, Bertagna X, Fournier C, Guiban D, Luton JP 1995 Long-distance and long-term follow-up of a patient with intermittent Cushing's disease by salivary cortisol measurements. Eur J Endocrinol 133:313-316

31. Carroll T, Raff H, Findling JW 2008 Late-night salivary cortisol measurement in the diagnosis of Cushing's syndrome. Nature Clinical Practice Endocrinology & Metabolism 4:344-350

32. Raff H 2013 Update on late-night salivary cortisol for the diagnosis of Cushing's syndrome: methodological considerations. Endocrine 44:346-349

33. Biller BM, Grossman AB, Stewart PM, Melmed S, Bertagna X, Bertherat J, Buchfelder M, Colao A, Hermus AR, Hofland LJ, Klibanski A, Lacroix A, Lindsay JR, Newell-Price J, Nieman LK, Petersenn S, Sonino N, Stalla GK, Swearingen B, Vance ML, Wass JA, Boscaro M 2008 Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. The Journal of Clinical Endocrinology and Metabolism 93:2454-2462

34. Barker FG, 2nd, Klibanski A, Swearingen B 2003 Transsphenoidal surgery for pituitary tumors in the United States, 1996-2000: mortality, morbidity, and the effects of hospital and surgeon volume. The Journal of Clinical Endocrinology and Metabolism 88:4709-4719

35. Gittoes NJ, Sheppard MC, Johnson AP, Stewart PM 1999 Outcome of surgery for acromegaly--the experience of a dedicated pituitary surgeon. QJM 92:741-745

36. Tritos NA, Biller BM 2014 Medical management of Cushing's disease. Journal of Neuro-oncology 117:407-414

Nicholas Tritos has no relationships to disclose.

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

Use of Genomics in Elucidating Puberty

Nelly Pitteloud

CHUV, Centre hospitalier universitaire vaudois, Service d'Endocrinologie, Diabétologie et Métabolisme, Lausanne, Switzerland

Isolated gonadotropin-releasing hormone (GnRH) deficiency caused by defective secretion or action of hypothalamic GnRH is a rare genetic disease that manifests as sexual immaturity and infertility. Over the past decade, the accelerating pace of genetic discovery has enhanced our understanding of the molecular basis of CHH with more than 25 loci associated with this condition to date. CHH was considered to be a Mendelian disorder. Reports of patients who harbor pathogenic rare variants in more than one gene have challenged the long-held view that the disorder is strictly monogenic. By systematically defining rare variants in large cohorts of well-phenotyped CHH patients, it became clear that oligogenicity plays a significant role in this disease. Next generation sequencing is expanding our understanding of the molecular mechanisms underlying disorders of puberty.

Nelly Pitteloud has no relationships to disclose.

What's the Latest on Endocrine Effects of Traumatic Brain Injury?

Christopher Thompson

Beaumont Hospital, Department of Endocrinology, Dublin, Ireland

1. **Acute TBI and hypopituitarism**

   Post mortem studies show a significant incidence of pituitary infarction in fatal TBI. This is the pathophysiological basis behind some of the clinical observations of abnormal pituitary function following TBI. Although hyperprolactinaemia is a stress response and acute downregulation of the hypothalamo-pituitary gonadal axis is common to most intubated patients, the acute hypocortisolaemia seems to be a genuine function of pituitary dysfunction. Low plasma cortisol may occur in 80% of cases of acute TBI and although transient in most, it may lead to hypotension, hypoglycaemia, hyponatraemia, and it predicts mortality. In addition, some patients are left with permanent cortisol deficiency. The value of glucocorticoid replacement is unproven in RCTs but pending research data which suggests otherwise, we empirically treat plasma cortisol concentrations which are not appropriately raised for acute illness (<11 ng/ml or < 300nmol/l) with steroid cover.

2. **Chronic survivors of TBI.**

   The literature contains divided opinion on the true incidence of hypopituitarism in survivors of TBI, which reflects differences in methodology, particularly severity of brain injury, and methods of testing. Danish data would strongly suggest that pituitary dysfunction is rare after mild TBI but most robust studies using gold standard testing suggests pituitary dysfunction of varying severity in 20-30% of cases.

3. **Who to test**

   I shall discuss the utility of guidelines for whom to test, with reference to new (unpublished) data from our own unit.

Christopher Thompson has no relationships to disclose.

PITUITARY TUMORS

Chair: John Newell-Price

Management of Nelson's Syndrome and Invasive Corticotroph Tumors

Kalmon D. Post

Icahn School of Medicine at Mount Sinai, New York, NY, USA

Nelson's syndrome and invasive corticotroph tumors can be very aggressive and taxing to treat with adequate control. The pathophysiology will be reviewed as well as current pathology tumor markers as an indication of aggressiveness. Surgery remains the first line of therapy and endoscopic techniques allow more radical resection of tumors invading the medial aspect of the cavernous sinus. Radiation with sterotactic radiosurgical techniques are often required in addition to medical therapies. Results with cabergoline, pasireotide, and Temozolomide will be reviewed. An algorithm for treatment will be presented.

Kalmon Post has no relationships to disclose.

Macroprolactinemia Revisited

Andrea Glezer

Neuroendocrine Unit, Division of Endocrinology and Metabolism, Hospital das Clinicas de Sao Paulo and Clinical Researcher at Laboratory of Celular and Molecular Endocrinology LIM25 University of Sao Paulo Medical School, Sao Paulo, Brazil

According to its isoforms molecular weight, serum prolactin (PRL) is classified in monomeric PRL (mPRL), dimeric or big PRL (bPRL), and macroprolactin or big big PRL (bbPRL). Usually, the predominant circulating isoform is mPRL, however in macroprolactinemia, bbPRL is the preponderant one. Although chromatography is the gold standard for diagnosis of macroprolactinemia, screening is routinely performed by polyethylenoglycol (PEG) precipitation. Macroprolactin is composed in most cases by an IgG that specifically binds to mPRL; nevertheless the mechanisms involved in IgG anti-PRL generation are still not clarified. Hyperprolactinemia secondary to macroprolactinemia could be due to its lower clearance with consequent longer half-life, as well as to its lower biological activity and less stimulation of hypothalamic dopaminergic tonus, as compared to mPRL. Prevalence of macroprolactinemia in hyperprolactinemic patients ranges between 15 to 46%, mean 25%. Most studies evaluating symptoms in macroprolactinemic individuals pointed to the low biological activity of bbPRL in vivo. In species-specific bioassays. bbPRL also presented low activity. However, some individuals with macroprolactinemia can also present high levels of mPRL, which could explain their symptoms. Therefore, standardization of normal mPRL levels after PEG precipitation is important to identify those patients with true hyperprolactinemia. Nevertheless, most individuals with macroprolactinemia are asymptomatic; being its detection crucial to avoid unnecessary treatment. We propose a flowchart to evaluate individuals with macroprolactinemia.

Andrea Glezer has no relationships to disclose.

Targeted Therapy for Aggressive Pituitary Tumors

Odelia Cooper

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

Although usually benign, 0.2% of pituitary adenomas may become aggressive carcinomas with median survival of 12 months. Atypical adenomas, identified in 15% of pituitary adenomas tend to present with a more aggressive clinical course resistant to standard therapies. Complications of each additional surgery and radiotherapy for these tumors include development of new onset hypopituitarism, cerebrospinal fluid leak and fistulas, meningitis, vascular and cranial nerve injury, cognitive deterioration, and visual field compromise. Therapeutic targeting of new molecular pathways shown to be involved in pituitary tumorigenesis may potentially reduce morbidity and mortality from these tumors and their treatment. Temozolomide has been reported in treatment of aggressive tumors, with the highest response rates in ACTH secreting tumors. Addition of capecitabine to temozolomide is beginning to be used successfully in ACTH adenomas. A second potential target is the EGFR family. Lacto-somatotroph and corticotroph derived tumors express ErbB receptors and ligands, and targeting this system affects PRL and ACTH gene expression, secretion, and tumor size. Early results from an ongoing clinical trial suggest PRL reduction and tumor stability in resistant prolactinomas with treatment of lapatinib, a dual EGFR/Her2 tyrosine kinase inhibitor. Finally, a CDK inhibitor, Roscovitine, has demonstrated preclinical efficacy in corticotroph animal models and is in clinical trials for patients with Cushing adenomas. These new molecular targeted therapies provide new avenues of therapy and await larger clinical studies for validation.

Odelia Cooper has no relationships to disclose.

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

Niki Karavitaki

Centre for Endocrinology, Diabetes and Metabolism, School of Clinical & Experimental Medicine, University of Birmingham, Birmingham, UK

A small percentage of pituitary adenomas show aggressive behaviour characterized by resistance to (multimodality) treatment with difficult hormonal control and/or imaging progression. The management of this group of tumors remains challenging and targeted therapy appears as a promising option on the horizon.

It has been shown that Akt expression and activity are constitutively increased in human pituitary tumors. Rapamycin and its orally available analog, RAD001 (Everolimus) reduce the viability of the rat pituitary tumour cell lines GH3 and MtT/S, as well as of cells from human GH-secreting pituitary adenomas in primary cultures. Furthermore, it has been demonstrated that RAD001 reduced the cell viability in 28/40 non-functioning pituitary adenomas dispersed in primary cultures and blocked IGF-I proliferative and antiapoptotic effects. Despite these in vitro data, published results on the efficacy of mTOR inhibitors in the management of aggressive pituitary adenomas are currently not available.

Anti-VEGF therapy aiming to prevent the formation of new vasculature and inhibit tumor growth appears to be another option but, apart from a case of pituitary carcinoma, experience in clinical practice is lacking.

Peptide receptor radionuclide therapy has been suggested as another approach with a limited number of published cases demonstrating tumor control; the toxicity to the normal brain tissue remains to be assessed.

The clarification of the pathways involved in the pathogenesis of pituitary tumors is opening further avenues in the development of drugs, particularly for challenging cases of pituitary adenomas; their efficacy and safety in clinical practice remains to be evaluated.

Niki Karavitaki has no relationships to disclose.

ROUND TABLE DISCUSSION – CRITICAL COMPARISONS OF MEDICAL THERAPIES FOR CUSHING'S DISEASE

Chair: Beverly MK Biller

Pasireotide

Annamaria Colao, Chiara Simeoli, Rosario Pivonello

Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università "Federico II" Naples, Italy

Pasireotide, a novel multi-receptor targeted somatostatin analogue, able to inhibit ACTH secretion via binding the subtype 5 somatostatin receptor (SSTR5), highly expressed in human corticotroph pituitary tumours, is the only pituitary-directed compound to have obtained the official approval for treatment of adults patients with Cushing's disease (CD) who experienced a failure of pituitary surgery or are not candidates for surgery and require medical therapeutic intervention. Pasireotide has been first evaluated in an open-label, multicenter phase II study in patients with de novo or persistent/recurrent CD (1). At the dose of 600 μg bid for 15 days, pasireotide induced UFC decrease in 76% and normalization in 17% of cases (1). A large randomized, double-blind phase III study has evaluated the effects of chronic treatment with pasireotide 600-900 μg bid in 162 patients with de novo or persistent/recurrent CD (2). After 6 months of therapy, 14.6% (600 μg) and 26.3% of patients (900 μg) have normalized UFC levels, without a prior dose increase (2). With the inclusion of patients who had an increase in drug dose, these percentages raised to 15.9% (600 μg) and 28.8% of patients (900 μg) (2). After 12 months, 13.4% (600 μg) and 25% of patients (900 μg) have maintained normal UFC (2). Moreover partial control of hypercortisolism has been achieved in 18.3% (600 μg) and 12.5 % of patients (900 μg) at month 6, and in 15.9% (600 μg) and 2.5% (900 μg) at month 12 (2). As overall, full and partial control was obtained in 34.2% (600 μg) and 41.3% of patients (900 μg) after 6 months and in 29.3% (600 μg) and 27.5% of patients (900 μg) after 12 months (2). Moreover, in the phase III clinical trial it has been reported that the reduction in UFC was associated with a significant improvement in body weight, blood pressure, lipid profile and health-related quality of life score (2). Interestingly blood pressure, BMI, body weight and waist circumference have been shown to significantly improve after treatment with pasireotide regardless from UFC normalization, even in patients not achieving full disease control (3). Conversely, total and LDL cholesterol have been found significantly reduced in patients who reached UFC control (3). More recently it has also been reported that pasireotide was able to maintain its effectiveness over 24 months of treatment: in fact of the 58 patients who entered the extension phase III study, 34.5% had controlled UFC levels at month 24 with a mean UFC reduction of 62.1%. Additionally marked improvements in clinical signs and symptoms of CD, mainly in systolic and diastolic blood pressure, body weight, BMI and total cholesterol level, were sustained until month 24 (4). The safety profile of pasireotide is typical for a somatostatin analogue, except for the frequency and degree of hyperglycemia. All previous studies (1-4) have consistently documented the impairment in glucose profile following pasireotide starting, requiring the addition or adjustment of proper antidiabetic treatment or definitive pasireotide discontinuation. Particularly, in the 12-month phase III study (2), hyperglycaemia-related adverse events have been reported in 73% of patients, requiring new antidiabetic treatment in 46% and inducing definitive pasireotide discontinuation in 6% of cases (2). Data published on patients treated with pasireotide up to the 24 months (4) demonstrated that hyperglycemia-related adverse events occurred in 79.1% of patients and that plasma glucose and HBA1c levels increased soon after initiation of pasireotide but did not deteriorate further over 24 months of treatment (4). Patients on pasireotide treatment should be monitored for changes in glucose metabolism and hyperglycemia. Diabetes mellitus should be managed by initiation of medical therapy with metformin and staged treatment intensification with a dipeptidyl peptidase-4 inhibitor, with a switch to a GLP-1 receptor agonist and initiation of insulin, as required, to achieve and maintain glycemic control (5).

1. Boscaro, M., et al: Treatment of pituitary dependent Cushing's disease with the multireceptor ligand somatostatin analog pasireotide (SOM230): a multicenter, phase II trial. J Clin Endocrinol Metab. 94, 115-22 (2009)
2. Colao, A., et al: Pasireotide B2305 Study Group. A 12-month phase 3 study of pasireotide in Cushing's disease. N Engl J Med. 366, 32-42 (2012)
3. Pivonello, R., et al: Pasireotide treatment significantly improves clinical signs and symptoms in patients with Cushing's disease: results from a Phase III study. Clin Endocrinol (Oxf) 81 (3), 408-17 (2014)
4. Schopohl, J., et al: Pasireotide can induce sustained decreases in urinary cortisol and provide clinical benefit in patients with Cushing's disease: results from an open-ended, open-label extension trial. Pituitary. 2014 Dec 24 [Epub ahead of print]
5. Colao, A., et al: Managing hyperglycaemia in patients with Cushing's disease treated with pasireotide: medical expert recommendations. Pituitary. 17, 180-186 (2014)

Annamaria Colao has no relationships to disclose.

Mifepristone

Maria Fleseriu

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

Medical treatment plays an important role for patients with Cushing's disease who have persistent or reccurent disease after surgery, for those in whom surgery is not feasible, or while awaiting effects of radiation. Multiple drugs, with different mechanisms of action and variable efficacy and tolerability are now available. Mifepristone (a glucocorticoid receptor antagonist) has been FDA- approved for treatment of hyperglycemia associated with Cushing's syndrome. Unlike other agents, mifepristone does not decrease cortisol levels, but directly antagonizes its effects. In a 6-month open- label trial on doses of 300 - 1,200 mg, 60% of patients with glucose intolerance or diabetes had at least 25% reduction in glucose on OGTT. Eight-seven percent of patients had significant improvement in clinical status. Changes in body weight, diastolic blood pressure, two-hour glucose post OGTT and cushingoid appearance were strong correlates of global clinical response improvement. In a more recent analysis that included longer- term data, a ≥2-fold increase in ACTH was observed in 72% of patients (treated for a median duration of almost a year). Concentrations of ACTH rose within the first few weeks of treatment and returned to near-baseline levels after discontinuation of therapy; levels directly correlated with mifepristone dose. Over the duration of the study, pituitary adenomas remained stable in 30/36 patients, regressed in 2 patients, and progressed in 4 patients. Of the 7 macroadenomas, 3 tumors remained stable, 1 regressed (after radiation therapy), and 3 continued to grow; however, 1 of the 3 progressive macroadenomas was aggressive before starting mifepristone. ACTH increases did not predict corticotroph tumor progression. Adverse effects include hypokalemia, endometrial thickening with vaginal bleeding and adrenal insufficiency. The lack of a biochemical marker dictates that efficacy and adrenal insufficiency assessments should be based on symptoms, clinical and metabolic features. The medical therapy of CD should be individualized; the choice between different medications is guided by patient characteristics, preference and availability.

References

1. Fleseriu M, Biller BM, Findling JW, Molitch ME, Schteingart DE, Gross C (2012) Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. J Clin Endocrinol Metab 97(6):2039-2049
2. Fleseriu M, Molitch ME, Gross C, Schteingart DE, Vaughan TB, 3rd, Biller BM (2013) A new therapeutic approach in the medical treatment of Cushing's syndrome: glucocorticoid receptor blockade with mifepristone. Endocr Pract 19(2):313-326
3. Nieman LK (2013) Update in the medical therapy of Cushing's disease. Curr Opin Endocrinol Diabetes Obes 20(4):330-334
4. Gadelha MR, Vieira Neto L (2014) Efficacy of medical treatment in Cushing's disease:a systematic review. Clin Endocrinol (Oxf) 80(1):1-12
5. Katznelson L, Loriaux DL, Feldman D, Braunstein GD, Schteingart DE, Gross C (2014) Global clinical response in Cushing's syndrome patients treated with mifepristone. Clin Endocrinol (Oxf) 80(4):562-569
6. Tritos NA, Biller BM, Medical management of Cushing's disease, J Neurooncol. 2014 May;117(3):407-14.
7. Fleseriu M, Findling JW, Koch CA, Schlaffer SM, Buchfelder M, Gross C (2014) Changes in plasma ACTH levels and corticotroph tumor size in patients with Cushing's disease during long-term treatment with the glucocorticoid receptor antagonist mifepristone. J Clin Endocrinol Metab 99(10):3718-3727

Maria Fleseriu receives consulting fees from Novartis and her institution receives research grants from Novartis and Cortendo.

Cabergoline Treatment of Cushing's Disease

Jérôme Bertherat

Center for Rare Adrenal Diseases, Cochin Hospital, Paris Descartes University, Paris, France

Medical treatment is currently used in about 40% of patients with Cushing's disease. In half of them as first line treatment, and in the remaining patients after pituitary surgery failure and/or radiation therapy.

Medical therapies of Cushing's disease can be divided in 3 groups: 1- Medications that target the pituitary corticotroph adenoma to inhibit ACTH secretion and reduce tumor growth. 2- Medications that directly act at the level of the adrenal cortex to inhibit cortisol secretion. 3- Medications that act at the periphery to block the cortisol receptor.

Cabergoline is one of the drugs that have been used to directly target the pituitary corticotroph adenoma. The rational for its use is the demonstration of the expression of Dopamine type 2 receptors (D2R) in more than three quarters of corticotroph tumors. In vitro studies have demonstrated that D2R expression correlates with inhibition of ACTH secretion by dopamine agonist in pituitary corticotroph tumor cells.

The efficacy of Cabergoline in Cushing's disease has been reported in various case reports and investigated only in a limited number of non randomized studies. Then to 30 patients have been analyzed in these studies. On the overall an optimal response, mostly based on normalization of Urinary Free Cortisol, is observed in 30 to 40% of the patients. One study reported normalization of midnight serum cortisol and/or cortisol after low dose dexamethasone suppression in 28% of the patients. In parallel, an improvement of glucose tolerance and blood pressure is observed. A tumor volume decrease is observed in a subset of patients. A significant reduction (i.e. > 25%) of volume might even be observed in up to half of the evaluable patients. However, short-term as well as long-term escape has been observed in some patients apparently initially responsive to treatment. Tolerability of Cabergoline in Cushing's disease seems favorable, no major side effect has been apparently reported.

The results of these various studies and case reports will be presented. The main advantages and disadvantages in terms of efficacy and safety of the use of Cabergoline in Cushing's disease will be discussed in the presentation.

Jérôme Bertherat has no relationships to disclose.

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

Adrenal Synthesis Inhibitors

Xavier Bertagna

Endocrinology Department, Centre de Référence des Maladies Rares de la Surrénale, Hôpital Cochin, Faculté de Médecine Cochin- Port-Royal, Université Paris 5, INSERM U-1016, Institut Cochin, Paris, France

The best neurosurgeon cannot always find a minute adenoma profoundly embedded in the pituitary gland, or entirely remove another adenoma which already has invasive features. Thus we have to cope with immediate failures and late recurrences, and make difficult choices between a large number of other options which all have definite drawbacks.

Among the medications which act directly at the adrenals we can distinguish two classes: The first include drugs which directly inhibit the enzymatic synthesis of cortisol. Their effect is immediate, but their long term efficiency is variable, and they may induce adverse events in relation with the overproduction of bioactive adrenal precursors, androgens and/or mineralocorticoids, under the pressure of exacerbated ACTH increase. Metyrapone and Ketoconazole have been the most frequently used until now. Yet, a new and highly powerful inhibitor of CYP11B1, LCI699, is under study and the recent results will be presented. The second class is represented by Lysodren (O, p', DDD) which acts in a different way being rather an adrenolytic drug. It has a slow onset of action, and many adverse events, and requires a good expertise for its long term management. Yet, in many patients it is very efficient leading to a "chemical adrenalectomy".

In severe cases, where rapid control of the hypercortisolism is needed, IV etomidate has been successfully used; alternatively a combination of Ketoconazole/Metyrapone/Lysodren has proved efficacious as well, within days.

Adrenal inhibitors have been proposed as adjunctive therapies to other treatment options directed at the pituitary, in preparation to pituitary surgery, or awaiting the full effect of pituitary radiotherapy.

All these aspects will be discussed, in a comparative fashion, considering the ultimate goals of treating Cushing's disease.

Xavier Bertagna receives consulting fees from Novartis.

PITUITARY TRANSLATIONAL BIOLOGY

Chair: William Farrell

Puberty Mechanisms

Ana Paula Abreu Metzger

Medicine, Division of Endocrinology, Diabetes & Hypertension, Brigham and Women's Hospital/ Harvard Medical School, Boston, MA, USA

Puberty is a complex temporal sequence of biological events leading to the maturation of secondary sex characteristics, accelerated linear growth, and attainment of reproductive capacity. Puberty and reproduction are controlled by the hypothalamic-pituitary-gonadal (HPG) axis. Hypothalamic gonadotropin-releasing hormone (GnRH) acts on the pituitary to stimulate the secretion of LH and FSH, which in turn act on the gonads to stimulate gametogenesis and the secretion of sex steroids. The HPG axis is active during the fetal and neonatal stages of life but subsequently inhibited during infancy. The removal of the inhibitory tone, together with an increase in excitatory inputs to GnRH neurons, culminate with puberty initiation. The precise mechanisms that trigger puberty initiation are not completely understood. This presentation will discuss the neuroendocrine regulation of puberty initiation.

Pubertal timing is influenced by complex interactions of genetic, nutritional, environmental and socioeconomic factors. The genetic determinants of the timing of human pubertal development are largely unknown. To date, the greatest insights into the mechanisms that regulate activation of GnRH secretion and therefore puberty initiation have been provided by the study of genetic abnormalities in patients with pubertal disorders. Idiopathic hypogonadotropic hypogonadism (IHH) is a condition characterized by failure to undergo puberty, with GnRH deficiency and low sex steroids. Several genes have been identified in association with IHH and have contributed to the current knowledge of GnRH regulation. On the other hand, early reactivation of GnRH secretion results in gonadotropin-dependent or central precocious puberty, defined clinically as the development of secondary sexual characteristics before age 8 years in girls and 9 years in boys. Genes linked to central precocious puberty have until recently only been identified subsequent to their association with IHH, such as KISS1 and KISS1R. Recently, with the development of new sequencing methodologies, a novel gene was identified associated with central precocious puberty, MKRN3.

MKRN3 is the first imprinted gene associated with an isolated pubertal disorder and the first gene identified with mutations in humans with an inhibitory effect on GnRH secretion. MKRN3 has no previous link with GnRH biology and its function is not known. Although the precise mechanism of regulation of GnRH secretion by MKRN3 is not yet well understood, its importance in the hypothalamic-pituitary-axis is indisputable and the elucidation of how MRKN3 regulates GnRH secretion will broaden the knowledge of puberty regulation.

Ana Paula Abreu Metzger has no relationships to disclose.

Mechanisms for Prolactin Regulation of Reproduction

Nadine Binart

INSERM U1185, Faculté de Médecine Paris Sud, Le Kremlin-Bicêtre Cedex, France

Hyperprolactinemia induced hypogonadotropic anovulation (PRL-HA) is a major cause of amenorrhea secondary to hypothalamic GnRH deficiency in women.

This gonadotropic deficiency has been proposed to result from direct suppression of prolactin (PRL) on GnRH release but its mechanism remains unknown. Because GnRH neurons do not express unequivocally the PRL receptor, and are stimulated by kisspeptin (Kp) neurons which do express PRL receptors, we hypothesized that GnRH deficiency in this condition could be due to a decrease in Kp secretion.

We developed and characterized a hyperprolactinemic female mouse model mimicking the human pathology and analyzed the ability of Kp administration to restore gonadotropin secretion and cyclicity. Then, we demonstrated that hypothalamic Kp expression was diminished and that Kp administration restored hypothalamic GnRH release, gonadotropin secretion, and ovarian cyclicity, suggesting that Kp neurons play a major role in PRL-HA. Altogether with the recent demonstration that Kp neurons express high levels of PRL receptor, our data suggest that PRL excess acts directly on Kp neurons to suppress Kp secretion and downstream GnRH secretion. Kp neurons appear, therefore, to be the missing link between hyperprolactinemia and GnRH deficiency.

Two hyperprolactinemic women with cabergoline resistant microadenomas (<6 mm), high serum PRL and with chronic secondary amenorrhea related to PRL-HA were studied to evaluate the effect of Kp administration on gonadotropic-ovarian axis. Blood samples were taken every 10 min for 12 h for measurement of LH, FSH and free α-subunit pulsatility, serum estradiol and inhibin B levels. Infusion of Kp induced a significant increase in pulsatile secretion of the two gonadotropins, and FAS with a dramatic rise in their amplitude. A rapid and very significant increase, in mean LH, FSH, but also in ovarian estradiol, inhibin B circulating levels occurred.

Therefore, we demonstrate that Kp administration can stimulate short term gonadotropin secretion in women with PRL-HA. This exploratory study suggests that Kp could be an alternative therapeutic approach to restore ovulation and fertility in hyperprolactinemic women resistant to dopamine agonists. Long-term clinical trials will be necessary to confirm the therapeutic relevance of Kp in clinical practice.

Nadine Binart has no relationships to disclose.

Pituitary Tumor Stem Cells

Cynthia-Lilian Andoniadou

Craniofacial Development and Stem Cell Biology, King's College London, Guy's Hospital, London, UK

The postnatal pituitary gland houses mixed populations of hormone-producing cells as well as lineage-committed progenitors. Among these is a small population of uncommitted cells that express SOX2, which have been identified as multipotent pituitary stem cells in vitro, but their physiological role in vivo and possible contribution to oncogenesis remain largely unknown. Using genetic lineage tracing in mouse, we show that the SOX2-expressing compartment contains progenitor/stem cells able to differentiate into all hormone-producing lineages and contribute to organ homeostasis during postnatal life. In addition, we demonstrate that when targeted to express oncogenic beta-catenin, these cells trigger the formation of pituitary tumors resembling adamantinomatous craniopharyngioma. Unexpectedly, the tumor mass is not derived from the mutation-sustaining pituitary stem cells, suggesting a paracrine mechanism promoting tumor formation. We provide in vivo evidence for the contribution of the SOX2 stem cell population in the long-term physiological cell turnover of the adult pituitary, as well as a novel mechanism implicating these cells in the induction of tumors in a non-cell autonomous manner.

Cynthia-Lilian Andoniadou has no relationships to disclose.

Acquired Adult Hypopituitarism

Thierry Brue

Endocrinology Service, Diabetes and Metabolic Diseases, and Original Rare Diseases Reference Center Pituitary DEFHY, Timone Hospital, Assistance Publique-Hôpitaux de Marseille and Aix-Marseille University, Marseille, France

Anterior Pituitary Hormone Deficiencies may be secondary to any lesion in this region, generally benign tumors like pituitary adenomas or craniopharyngiomas. Surgical or radiation-based treatments of these tumors are also among the most common causes of acquired hypopituitarism.

This presentation will mainly focus on less frequent causes of acquired adult hypopituitarism, such as cranial traumas, inflammatory or autoimmune processes like lymphocytic hypophysitis that may lead to pituitary deficits. Although genetic mechanisms are not primarily considered among causes of adult hypopituitarism they may be of delayed onset, thus appearing as "acquired" deficiency. These disorders represent a heterogeneous group of rare diseases leading to defective function of specific pituitary cell types. The resulting pituitary hormone deficiencies lead, if not treated in a timely fashion, to severe clinical consequences.

Hypophysitis is a chronic inflammation of the pituitary gland of unknown (primary forms) or recognizable (secondary forms) etiology, such as some cancer immunotherapy agents. In a recent study, we found that ipilimumab may induce hypophysitis in as many as >10% of treated patients (1). This monoclonal antibody blocks the T cell inhibitory molecule CTLA-4 (cytotoxic T lymphocyte antigen-4); the group of Caturegli demonstrated that the mechanism of ipilimumab-induced hypophysitis was similar to that seen in type II hypersensitivity (2).

The incidence of some classical causes of hypopituitarism such as Sheehan's syndrome has dramatically dropped with the improvement of obstetrical management standards in many countries, explaining why this etiology has become an overlooked cause in developed countries (3).

Among late onset genetic disorders that can be diagnosed in late childhood or into adulthood, we described the DAVID syndrome as an association of a deficit in adrenocorticotrophin and/or anterior pituitary hormones, with recurrent infections due to variable immunodeficiency (4). This condition is caused by mutations in the NFKB2 gene (5, 6). In recent years, other rare immune-related etiologies of acquired hypopituitarism have also been reported such as the anti-Pit1 antibody syndrome (7).

In conclusion, recognition of all causes and timely treatment of acquired adult hypopituitarism represents a challenge which is all the more relevant as recent studies have confirmed the increased mortality associated with this condition (8).

References

1: Albarel F, Gaudy C, Castinetti F, Carré T, Morange I, Conte-Devolx B, Grob JJ, Brue T. Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. Eur J Endocrinol. 2015 Feb;172(2):195-204.

2: Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med. 2014 Apr 2;6(230):230

3: Ramiandrasoa C, Castinetti F, Raingeard I, Fenichel P, Chabre O, Brue T, Courbière B. Delayed diagnosis of Sheehan's syndrome in a developed country: a retrospective cohort study. Eur J Endocrinol 2013 Sep 12; 169(4):431-8.

4: Quentien MH, Delemer B, Papadimitriou DT, Souchon PF, Jaussaud R, Pagnier A,Munzer M, Jullien N, Reynaud R, Galon-Faure N, Enjalbert A, Barlier A, Brue T. Deficit in anterior pituitary function and variable immune deficiency (DAVID) in children presenting with adrenocorticotropin deficiency and severe infections. J Clin Endocrinol Metab. 2012 Jan;97(1):E121-8.

5: Chen K, Coonrod EM, Kumánovics A, Franks ZF, Durtschi JD, Margraf RL, Wu W, Heikal NM, Augustine NH, Ridge PG, Hill HR, Jorde LB, Weyrich AS, Zimmerman GA, Gundlapalli AV, Bohnsack JF, Voelkerding KV. Germline mutations in NFKB2 implicate the noncanonical NF-κB pathway in the pathogenesis of common variable immunodeficiency. Am J Hum Genet. 2013 Nov 7;93(5):812-24.

6: Brue T, Quentien M, Khetchoumian K, Bensa M, Capo-Chichi J, Delemer B, Balsalobre A, Nassif C, Papadimitriou DT, Pagnier A, Hasselmann C, Patry L, Schwartzentruber J, Souchon P, Takayasu S, Enjalbert A, Van Vliet G, Majewski J, Drouin J, Samuels ME. Mutations in NFKB2 and potential genetic heterogeneity in patients with DAVID syndrome, having variable endocrine and immune deficiencies. BMC Med Genet. 2014 Dec 19;15(1):139.

7: Yamamoto M, Iguchi G, Takeno R, Okimura Y, Sano T, Takahashi M, Nishizawa H,Handayaningshi AE, Fukuoka H, Tobita M, Saitoh T, Tojo K, Mokubo A, Morinobu A, Iida K, Kaji H, Seino S, Chihara K, Takahashi Y. Adult combined GH, prolactin, and TSH deficiency associated with circulating PIT-1 antibody in humans. J Clin Invest. 2011 Jan;121(1):113-9.

8. Burman P, Mattsson AF, Johannsson G, Höybye C, Holmer H, Dahlqvist P, BerinderK, Engström BE, Ekman B, Erfurth EM, Svensson J, Wahlberg J, Karlsson FA. Deaths among adult patients with hypopituitarism: hypocortisolism during acute stress, and de novo malignant brain tumors contribute to an increased mortality. J Clin. Endocrinol Metab 2013 Apr; 98(4):1466-75.

Thierry Brue receives consulting fees/honoraria from Pfizer, Novartis, and Ipsen and research grants from Pfizer, Sandoz, and NovoNordisk.

HOT TOPICS

Co-Chairs: Marcello Bronstein and Ursula Kaiser

Rapid Remyelination Leads to Vision Recovery After Pituitary Tumor Resection

David Paul[1], Eric Hintz[1], Elon Gaffin-Cahn[1], Giscard Adeclat[1], Tong Zhu[2], Zoe Williams[1], Laura Calvi[1], G. Edward Vates[1], Bradford Mahon[1]

[1]University of Rochester School of Medicine and Dentistry, Rochester, NY, USA; [2]University of Michigan Medical Center, Ann Arbor, MI, USA

Introduction: The biologic basis of vision recovery after pituitary tumor resection is not known. Previous research that has looked at plasticity in the human brain using MRI in other diseases has focused on cortical reorganization in clinical populations for which functional recovery is limited. In this study, we show how structural and functional plasticity interact longitudinally in the adult human brain using a reversible lesion model – pituitary tumors that compress the optic chiasm. **Materials and Methods:** We used diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI) and visual psychophysical tests to longitudinally study a cohort of patients (N=9) undergoing removal of pituitary tumors compressing the optic chiasm as well patients with non-compressive pituitary tumors (N=5), and healthy controls (N=9). **Results:** Preoperative measures of optic tract myelination correlated with the degree of visual impairment before surgery. The demyelination of the optic tracts measured before surgery recovered as quickly as 4 weeks after tumor resection and nerve decompression. Furthermore, the amount of vision recovery correlated directly with recovery of myelin on the optic tracts; and preoperative measurements of myelination in the optic tracts predicted the magnitude of visual recovery after surgery. **Conclusions:** Vision recovery in patients after pituitary tumor resection results from rapid remyelination of the optic tracts. This model system of CNS repair shows that rapid regeneration of myelin in the human brain is a component of the recovery of sensory and cognitive function. These findings may help us better advise patients about vision recovery after pituitary tumor surgery. Moreover, patients with pituitary tumors offer a new window into longstanding questions about brain plasticity, both at the level of the white matter and the level of the cortex.

The authors have no relationships to disclose.

Efficacy and Safety of LCI699, a Potent 11β-hydroxylase Inhibitor, in Patients with Cushing's Disease: A 22-week, Multicenter, Open-label Study

Rosario Pivonello[1], Maria Fleseriu[2], Xavier Bertagna[3], Amir H Hamrahian[4], Mark E Molitch[5], Tomoaki Tanaka[6], Akira Shimatsu[7], Tracy White[8], Annie Hilliard[8], Nicholas Sauter[8], Beverly MK Biller[9]

[1]Dipartimento di Medicina Clinica e Chirurgia, Università Federico II di Napoli, Naples, Italy, [2]Northwest Pituitary Center, Departments of Medicine and Neurological Surgery, Oregon Health and Science University, Portland, OR, USA, [3]Department of Endocrinology, Centre de Référence des Maladies Rares de la Surrénale, Hôpital Cochin, Faculté de Médecine Paris Descartes, Université Paris 5, Paris, France, [4]Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic Foundation, Cleveland, OH, USA; [5]Division of Endocrinology, Metabolism and Molecular Medicine, Northwestern University, Chicago, IL, USA, [6]Division of Endocrinology and Metabolism, Chiba University Hospital, Chiba-city, Chiba, Japan, [7]Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto, Japan, [8]Novartis Pharmaceuticals, East Hanover, NJ, USA, [9]Neuroendocrine Clinical Center, Massachusetts General Hospital, Boston, MA, USA

Background: In a previous study (LINC 1), oral administration of the 11β-hydroxylase inhibitor LCI699 normalized UFC levels in 11/12 Cushing's disease patients after 10 weeks of treatment. Here, we report the efficacy and safety of LCI699 in 19 patients enrolled into a longer-term study (LINC 2; ClinicalTrials.gov identifier: NCT01331239). **Methods:** The follow-up cohort (n=4) included patients previously enrolled in LINC 1 who had not received LCI699 for ≥8 months and were then offered re-enrollment if their baseline UFC levels were >1 × ULN. The expansion cohort (n=15) included newly enrolled patients with baseline UFC levels >1.5 × ULN. The main efficacy endpoint was response, defined as controlled (mean UFC ≤ULN or ≥50% decrease from baseline) or uncontrolled (mean UFC >ULN and <50% reduction from baseline) at weeks 10 and 22. UFC levels were calculated from the means of at least two 24-hour urine collections, measured using LC MS/MS in a central laboratory. **Results:** Of 19 patients enrolled (female, n=14 [74%]; mean age [SD], 36.8 years [8.4]), 15 (78.9%) were controlled and 2 (10.5%) were uncontrolled at 22 weeks; 2 discontinued early. All patients controlled at 22 weeks had UFC ≤ULN and decreases in mean serum cortisol levels to within the normal range. Seven (36.8%) and 6 (31.6%) patients had increased levels of adrenal precursors and ACTH, respectively. Testosterone levels were above normal in 75% of women (n=9) who completed 22 weeks. The most common AEs were asthenia, nausea, diarrhea, and adrenal insufficiency. Two patients developed serious AEs (gastroenteritis and QT prolongation, n=1; uncontrolled disease, n=1). One patient discontinued for AEs (diarrhea, nausea, muscular weakness, malaise, and papule) and another for administrative issue. Nine patients experienced mild hypokalemia, and 6 experienced hypocortisolism-related AEs. **Conclusions:** Twenty-two weeks of LCI699 treatment reduced UFC levels to ≤ULN in 78.9% of patients and was well tolerated.

Xavier Bertagna receives consulting fees from Novartis; Beverly MK Biller receives honoraria from Cortendo and Novartis and her institution receives research grants from Cortendo and Novartis; Maria Fleseriu receives consulting fees from Novartis and her institution receives research grants from Cortendo and Novartis; Annie Hilliard, Nicholas Sauter, and Tracy White are Novartis employees; Mark

Molitch receives consulting fee and research support from Novartis; Rosario Pivonello receives consulting fees, honoraria and research support from Novartis; Akira Shimatsu receives honoraria from Novartis; the other authors have no relationships to disclose.

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

Human Folliculostellate Cell Line PDFS Facilitates the Formation of Tumor-like Structures in Human Pituitary Tumor Primary Cultures

Xun Zhang, Xiaobing Jiang, Karrin Weisenthal, Jun Ma, Yunli Zhou, Xianling Wang, Brooke Swearingen*, Michael Culler, Anne Klibanski**

*Neuroendocrine Unit, and *Neurosurgical Service, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; **Ipsen Bioscience, Inc., Cambridge, MA, USA*

One of the major obstacles in pituitary tumor study and drug development is the lack of a human model system. There is no reliable human pituitary tumor cell line. Primary cultures of human pituitary adenoma cells was widely used; however, these cultures are difficult to perform, often accompanied with fibroblasts. In addition, the human primary pituitary tumor cells are slow growing, rendering them unfavorable for addressing issues of cell proliferation and tumor growth. We have developed a human folliculostellate cell line, PDFS, spontaneously derived from a human clinically non-functioning pituitary adenoma. In the normal pituitary, folliculostellate cells are known to be involved in autocrine/paracrine regulation of anterior pituitary functions via secretion of growth factors and cytokines, intra-pituitary communication of different pituitary cell types, and modulation of inflammatory response. They therefore provide unique insights into the pituitary tumor microenvironment It has been shown that a subset of pituitary adenomas have significant numbers of folliculostellate cells, although detailed studies on the presence and functions of folliculostellate cells in human pituitary tumors are lacking. We hypothesize that in human pituitary adenomas, folliculostellate cells play a role in regulating cell growth and tumor formation. Therefore, we have developed a co-culture system by mixing the human folliculostellate cell line, PDFS, with human primary pituitary adenoma cells. We observed that in the presence of PDFS cells, human primary pituitary tumor cells aggregated to form colonies, and, together with PDFS cells, form three-dimensional, tumor-like structures. In contrast, no such tumor-like structures were formed when human primary pituitary adenoma cells were co-cultured with other cell lines such as human breast and brain cancer cells and rodent pituitary tumor cell lines. Using cell dividing inserts, we found that during primary culture, human primary pituitary adenoma cells migrated towards the neighboring PDFS cells, suggesting that PDFS cells secrete factors facilitating the movement of human primary pituitary adenoma cells and attracting them to PDFS cells. Our data suggest that folliculostellate cells play a critical role in human pituitary tumor formation and growth. The PDFS-primary pituitary tumor co-culture can be a useful tool for the study of mechanisms for human pituitary tumor pathogenesis as well as for screening novel therapeutics for human pituitary tumors.

Anne Klibanski receives grant support from Ipsen, Novartis and Rhythm Pharmaceuticals.

The other authors have no relationships to disclose.

X-Linked Acro-Gigantism (X-LAG) Syndrome: A New Form of Infant-onset Pituitary Gigantism

Constantine A Stratakis[1], Giampaolo Trivellin[1], Liliya Rostomyan[2], Maya Beth Lodish[1], Fabio R Faucz[1], Bo Yuan[3], Luciana Ansaneli Naves[4], Catherine S Choong[5], Philippe A Lysy[6], Nalini Samir Shah[7], Elisa Verrua[8], Jean-Hubert Caberg[9], Emilie Castermans[9], Mauricette Jamar[9], Maria Chiara Zatelli[10], Marie Helene Schernthaner-Reiter[1], Chiara Villa[2, 11], Daniel Metzger[12], Natalia Strebkova[13], Nadia Mazerkina[14], Tim D Cheetham[15], Maria Rosaria Ambrosio[10], Prashant Chittiboina[16], Stephan Gaillard[11], Gustavo Barcelos Barra[17], Eva Szarek[1], Leticia Ferro Leal[1], Aggeliki Dimopoulos[1], Paraskevi Xekouki[1], Anelia Dafinova Horvath[1], Rodrigo Bertollo de Alexandre[1], Allison D Manning[1], Isaac Levy[1], Margaret Keil[1], Maria De La Luz Sierra[1], Leonor Palmeira[18], Vincent Bours[9], Martha M. Quezado[19], Pengfei Liu[3], James R Lupski[3, 20], Adrian F. Daly[2], Albert Beckers[2]

[1]Program on Developmental Endocrinology and Genetics, Section on Endocrinology & Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), Bethesda, MD, USA, [2]Department of Endocrinology, University of Liège, Liège, Belgium; [3]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA, [4]Department of Endocrinology, University of Brasilia, Brasilia, Brazil, [5]Dept of Pediatric Endocrinology and Diabetes, Princess Margaret Hospital for Children, Subiaco WA, Australia, [6]Pediatric Endocrinology Unit, Université Catholique de Louvain, Bruxelles, Belgium, [7]Department of Endocrinology, KEM Hospital, Mumbai, India, [8]Endocrinology and Diabetology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy, [9]Department of Clinical Genetics, Centre Hospitalier Universitaire de Liège, University of Liège, Liège, Belgium, [10]Dept of Medical Sciences, Section of Endocrinology, University of Ferrara, Ferrara, Italy, [11]Hopital Foch, Suresnes, France, [12]Endocrinology and Diabetes Unit, BC Children's Hospital, Vancouver, BC, Canada, [13]Endocrinological Research Centre, Institute of Pediatric Endocrinology, Moscow, Russia, [14]Burdenko Neurosurgery Institute, Moscow, Russia, [15]Department of Paediatric Endocrinology, Royal Victoria Infirmary, Newcastle University, Newcastle upon Tyne, United Kingdom, [16]Surgical Neurology Branch, National Institute of Neurological Diseases and Stroke (NINDS), National Institutes of Health, Bethesda, MD, [17]Laboratorio Sabin, Brasilia, Brazil, [18]GIGA-Genomics, Liège, Belgium, [19]Laboratory of Pathology, National Cancer Institute, Bethesda, MD, USA, [20]Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

Introduction: Gigantism is a rare and dramatic clinical disorder; its etiology is usually unknown as AIP mutations only explain about one third of cases. X-linked Acro-gigantism (X-LAG) is a new syndrome caused by microduplications of an approximately 500 kb region on chromosome Xq26.3. Individuals with XLAG have a remarkably consistent phenotype of early onset gigantism due to mixed GH/PRL secreting pituitary macroadenomas +/- hyperplasia. The patients with X-LAG have a common shared region of overlap involving 4 coding genes, of which only one gene (GPR101) is highly upregulated in pituitary tumors. **Methods:** We performed an international study of confirmed X-LAG syndrome cases to characterize the genotype, clinical phenotype and responses to therapy. **Results:** The study included 16 patients with X-LAG and a microduplication in chromosome Xq26.3. Eleven cases were sporadic and another 5 cases belonged to 2 families that originally presented with FIPA. All sporadic cases had unique duplications, whereas the familial cases inherited identical duplications. The inheritance pattern was dominant. Patients were born at full-term and were of normal length, weight and head circumference and apart from the familial cases generally had parents and siblings of normal height. Patients with X-LAG syndrome began to grow rapidly during early childhood, in most cases rapid gain in length was noted between 6-18 months of age. At diagnosis (median 36 months), patients had a median height and weight SDS score of >+3. On presentation apart from the increased overall body size, the children had coarsening of facial features and enlargement of extremities. Snoring or sleep apnea was reported also, while about a quarter of cases had an eating disorder (food seeking behavior). All patients had marked hypersecretion of GH, IGF-1 and prolactin. All but one patient had a pituitary macroadenoma at diagnosis, the remaining patient only had marked hyperplasia and one patient had yet to be operated on. The pituitary tumors were positive for GHRH-R. Primary neurosurgical control was not achieved except in cases where gross anterior hypophyseal resection was performed and postoperative hypopituitarism was frequent. Responses to medical therapy with somatostatin analogs and dopamine agonists were poor; 4 patients received radiotherapy. Postoperative adjuvant pegvisomant achieved control of IGF-1 in the 5 cases in which it was employed. Final height has not been reached in 12/16 cases that are still in childhood/adolescence. **Conclusions:** X-LAG is a new infant-onset gigantism syndrome due to a microduplication in chromosome Xq26.3, including the gene GPR101. It is characterized by a severe clinical phenotype with disease onset usually at <3 years of age; the young age and the aggressive tumor behavior makes for very challenging disease management. CAS, GT, AFD, AB equal contribution

James Lupski is a consultant for 23andME and Ion Torrent Systems, Inc., is on the Board of Directors of Lasergen and is on the Scientific Advisory Board of Regeneron.

The other authors have no relationships to disclose.

GENETICS

Co-Chairs: Marcello Bronstein & Ursula Kaiser

AIP Mutations: Who Should We Screen?

Albert Beckers

University of Liège, Belgium

Genetic testing strategies in endocrine tumor patients are becoming ever more complicated due to the identification of new genetic risk factors. We are now seeing this beginning to impact patients with pituitary adenomas. AIP mutations are one of a growing number of genetic and genomic abnormalities that need to be considered in certain patients. Since its identification in 2006, numerous studies have been published examining the role of AIP in the etiology of different groups of pituitary adenoma patients. Taking these results together, groups of patients who have an elevated likelihood of having AIP abnormalities can be distinguished. These groups include Familial Isolated Pituitary Adenoma (FIPA) kindreds, pediatric and adolescent patients with macroadenomas and patients with pituitary gigantism. In addition, some clinical features of AIP mutation associated pituitary adenomas could help guide decisions to test in other patients. For instance, AIP abnormalities usually cause somatotropinomas, prolactinomas and non-functioning adenomas. Also, clinical responses to treatment in AIP mutation associated pituitary adenomas can be relatively poor, for instance responses to somatostatin analogues in those with acromegaly. There is little use in undertaking unselected general sequencing of pituitary adenoma populations. Abnormalities in AIP are not limited to sequence changes, but deletions of all or part of the gene have been well described. Hence screening strategies need to use techniques like MLPA to identify deletions in those high-risk patients with a normal AIP sequence. Once identified in a patient, the most challenging issue is how to proceed with screening in relatives. As AIP has a low overall penetrance (20%), counseling should include discussion regarding low probable lifetime risk. Testing for known AIP mutations/deletions in family members can help to narrow significantly the number of patients that require clinical follow-up; this is probably a resource efficient initial step.

Testing strategies for AIP abnormalities have to take account of other genetic causes of pituitary adenomas. For instance, MEN1 mutations can present with a pituitary adenoma alone (without overt parathyroid disease) in young patients. Also amongst the young with gigantism (either as FIPA or sporadic), genomic causes like the Xq26.3 microduplication seen in X-LAG syndrome need to be considered in parallel with AIP testing.

Albert Beckers has no relationships to disclose.

POSTER PRESENTATIONS

APPETITE/OBESITY

P1
Childhood Craniopharyngioma – Changes of Treatment Strategies in KRANIOPHARYNGEOM 2000/2007

Anika Hoffmann[1], Monika Warmuth-Metz[2], Ursel Gebhardt[1], Torsten Pietsch[3], Fabian Pohl[4], Rolf-Dieter Kortmann[5], Gabriele Calaminus[6], Hermann L. Müller[1]

[1]Dep. of Pediatrics, Klinikum Oldenburg, Medical Campus University Oldenburg, Oldenburg; [2]Dep. of Neuroradiology, University Hospital Würzburg; [3]Institute for Neuropathology, University of Bonn; [4]Dep. of Radiooncology, University Hospital Regensburg; [5]Dep. of Radiooncology, University of Leipzig; [6]Dep. of Pediatric Oncology, University Hospital Münster; Germany. On behalf of the study committee KRANIOPHARYNGEOM 2000/2007 (www.kraniopharyngeom.net)

Background: Despite high survival rates in childhood craniopharyngioma, prognosis is frequently impaired due to sequelae. Radical surgery was the treatment of choice for several decades. However, even at experienced surgical facilities radical surgery can result in hypothalamic disorders such as severe obesity. **Objective:** We analyzed, whether treatment strategies for childhood craniopharyngioma patients recruited in German studies (KRANIOPHARYNGEOM 2000/2007) have changed during the last 12 years. **Materials and methods:** We compared the grade of pre-surgical hypothalamic involvement, the treatment, degree of resection and grade of surgical hypothalamic lesions between patients recruited in KRANIOPHARYNGEOM 2000 (n=120; 2001-2007) and KRANIOPHARYNGEOM 2007 (n=106; 2007-2012). **Results:** The grade of initial hypothalamic involvement was similar in patients treated 2001-2007 and 2007-2012. The degree of resection was more radical (p=0.01) in patients recruited 2001-2007 (38%) when compared with patients treated 2007 to 2012 (18%). In patients with pre-surgical involvement of anterior/posterior hypothalamic areas, the rate of hypothalamus-sparing operations resulting in no (further) hypothalamic lesions was higher (p=0.005) in patients treated 2007 to 2012 (35%) in comparison with the 2001-2007 cohort (13%). Event-free-survival rates were similar in both cohorts. **Conclusions:** A trend towards less radical surgical approaches is observed, which was accompanied by a reduced rate of severe hypothalamic lesions. Event-free survival was not compromised by this development. Radical surgery is not an appropriate treatment strategy in patients with hypothalamic involvement. Despite previous recommendations to centralize treatment at specialized centers, a trend towards further decentralization was seen. Treatment should be confined to experienced multidisciplinary teams.

The authors have no relationships to disclose.

P2
Diencephalic Syndrome in Childhood Craniopharyngioma — Results of German Multicenter Studies on 485 Long-term Survivors of Childhood Craniopharyngioma

A Hoffmann[1], U Gebhardt[1], AS Sterkenburg[1,2], M Warmuth-Metz[3], HL Müller[1], on behalf of the study committees HIT Endo, KRANIOPHARYNGEOM 2000/2007 (www.kraniopharyngeom.net)

[1]Department of Pediatrics, Klinikum Oldenburg, Medical Campus University Oldenburg, Oldenburg, Germany; [2]Rijksuniversiteit Groningen, Groningen, The Netherlands; [3]University of Würzburg, Department of Neuroradiology, Würzburg, Germany

Context: Childhood craniopharyngiomas are known to be associated with an increased risk of excessive weight gain and hypothalamic obesity. Atypical clinical manifestations include the development of a diencephalic syndrome (DS) with a failure to thrive or weight loss. **Cases and Methods:** In a retrospective study we analyzed 21 of 485 childhood craniopharyngioma patients (4.3%) who presented with a low weight (<-2 BMI SDS) at time of diagnosis. 11 of 21 patients were identified with a DS due to proven hypothalamic involvement. We demonstrate the clinical manifestations of DS and weight development before and after diagnosis in these 11 patients. First significant differences between patients with low weight at diagnosis and normal weight patients at diagnosis are observed at an age of 5 years. Within the first 2 years after diagnosis, the weight of DS patients and normal weight patients converge to a similar level. Tumor size does not play a role in respect of DS development. Finally, MRI tumor properties of DS patients were compared with MRI scans of obese patients at time of diagnosis. A trend towards a lower rate of infiltrative growth within the hypothalamus might be related to DS patients. **Conclusions:** DS is a rare clinical manifestation in childhood craniopharyngioma but should be considered as a differential diagnosis in failure to thrive. DS at the time of diagnosis does not prevent weight gain after diagnosis of a craniopharyngioma with hypothalamic involvement.

The authors have no relationships to disclose.

P3

Eating Behavior and Weight Problems in Long-term Survivors of Childhood Craniopharyngioma – Results of the HIT ENDO Trial

A Hoffmann[1], FP Postma[1,2], U Gebhardt[1], HL Müller[1]

[1]Department of Pediatrics, Klinikum Oldenburg, Medical Campus University Oldenburg, Oldenburg, Germany; [2]University of Groningen, The Netherlands

Background: Due to hypothalamic tumour involvement and/or treatment related hypothalamic damage, up to 75% of childhood craniopharyngioma patients (CP) develop hypothalamic obesity. **Methods:** In this case-control study, eating behaviour and psychological assessment of weight problems in 102 CP patients, recruited between 1980 and 2001 in the HIT Endo trial, were analysed as well as a gender-, age- and BMI-matched healthy control group (n=61). Assessment of eating behaviour was performed by the "Inventory for Eating Behaviour and Weight Problems (IEG)" questionnaire. **Results:** CP patients were divided into a normal weight group (BMI<+3SDS; n=49) and an obese group (BMI>+3SD; n=53). Obese CP showed less pathological eating behaviour for the IEG domains "food intake on special occasions" (p=,008), "eating as a means of coping with emotional stress" (p=,049), "eating style" (p=,000), "pressure to eat during childhood" (p=,007), "bulimia" (p=,024), "feelings of constraint whilst eating out" (p=,001), and "interpersonal seclusion" (p=,006) when compared to 37 BMI-matched obese controls. Only for the domain 'restrains due to being overweight' obese CP scored worse then matched overweight controls (p=,001). Obese and normal weight CP answered the IEG quite similar. The comparison of 49 normal weight CP with 24 normal weight matched controls showed similar results except for the domains "eating style" (p=,018), "pressure to eat during childhood" (p=,041) and "perfectionism and achievement of goals (,015), for which CP scored higher e.g. had less pathological findings. **Conclusion:** Obese CP patients score better or non-different to obese controls on 22 of 23 IEG domains. We conclude that there is no disease-specific disturbance of eating behaviour in CP. We hypothesize, that severe obesity in CP might be the result of hypothalamic involvement/damage but not of disease-specific alterations in eating behaviour.

The authors have no relationships to disclose.

P4

Hydrocephalus or Hypothalamic Involvement in Pediatric Patients with Craniopharyngioma or Cysts of Rathke's Pouch: Impact on Long-term Prognosis

AMM Daubenbüchel[1,2], A Hoffmann[1], M Warmuth-Metz[3], U Gebhardt[1], AS Sterkenburg[1,2], HL Müller[1]

[1]Department of Pediatrics, Klinikum Oldenburg, Medical Campus University Oldenburg, Oldenburg, Germany; [2]University of Groningen, UMCG, The Netherlands; [3]University of Würzburg, Department of Neuroradiology, Würzburg, Germany

Objective: Pediatric patients with sellar masses such as craniopharyngioma (CP) or cyst of Rathke's pouch (CRP) frequently suffer disease- and treatment-related sequelae. We analyzed the impact and prognostic relevance of initial hydrocephalus (HY) and hypothalamic involvement (HI) on long-term survival and functional capacity (FC) in children with CP or CRP sellar masses. **Subjects and methods:** Using retrospective analysis of patient records, presence of HY or HI at primary diagnosis was assessed in 177 pediatric patients (163 CP, 14 CRP). Twenty-year overall survival (OS) and progression-free survival (PFS), FC, and body mass index (BMI) SDS were analyzed with regard to initial HY or HI. **Results:** 105 patients (103/163 CP, 2/14 CRP) presented with initial HY and 96 presented with initial HI. HY at diagnosis was associated with papilledema (p=0.000), neurological deficits (p=0.000), and higher BMI at diagnosis (p=0.001) and during follow-up (p=0.000). OS, PFS, and long-term FC were not affected by HY at initial diagnosis. HI at diagnosis (96/177) had major negative impact on long-term prognosis. Sellar masses with HI were associated with lower OS (0.84±0.04; p=0.021), lower FC (p=0.003), and higher BMI at diagnosis and last follow-up (p=0.000) when compared with sellar masses without HI (OS:0.94±0.05). PFS was not affected by HI. **Conclusions:** Initial HY has no impact on long-term survival in sellar masses. OS and FC are impaired in survivors presenting with initial HI. PFS is not affected by HY or HI. Accordingly, gross-total resection is not recommended in sellar masses with initial HI to prevent further hypothalamic damage.

The authors have no relationships to disclose.

P5

Survival, Hypothalamic Obesity and Neuropsychological / Psychosocial Status After Childhood-onset Craniopharyngioma – Long-term Results in 261 Patients Recruited in HIT Endo

AS Sterkenburg[1],[2], A Hoffmann[1], M Warmuth-Metz[3], U Gebhardt[1], AMM Daubenbüchel[1],[2], HL Müller[1]

[1]Department of Pediatrics, Klinikum Oldenburg, Medical Campus University Oldenburg, Oldenburg, Germany, [2]Rijksuniversiteit Groningen, Groningen, The Netherlands, [3]University of Würzburg, Department of Neuroradiology, Würzburg, Germany

Background: Quality of life and prognosis are frequently impaired in childhood-onset craniopharyngioma (CP) patients. Knowledge of risk factors for long-term outcome and sequelae after 20 years follow-up could help to improve actual treatment. **Patients and methods:** Cross-sectional study on overall (OS) and progression-free survival (PFS), body mass index (BMI) SDS, neuropsychological (EORTCQLQ-C30, MFI-20) and psychosocial status in 261 long-term survivors of CP recruited in the German CP registry (HIT Endo). **Results:** 20-yrs OS in CP patients (n=261, 0.88±0.03) was lower (p=0.006) in CP patients with HI (n=132,0.84±0.04) when compared to CP patients without HI (n=82, 0.95±0.04). OS was not related to degree of resection, gender, age or year at diagnosis (before/after 1990). PFS (n=168, 0.58±0.05) was lower in younger CP (age <5 yrs at diagnosis) (n=30, 0.39±0.10) compared with patients of 5-10 yrs of age (n=66, 0.52±0.08), and >10 yrs of age (n=72, 0.77±0.06). No association of PFS was detectable with HI, degree of surgical resection and gender. CP with HI developed severe weight gain during the first 8-12 yrs of follow-up (median increase in BMI: +4.59 SD; range -0.40 to +11.15 SD) when compared to CP without HI (median increase in BMI: +1.20 SD; range -1.19 to +5.02 SD) (p=0.00). During follow-up of >12 yrs, patients with HI presented no further increase in BMI SDS. QoL in CP with HI was impaired due to physical fatigue, reduced motivation and diarrhea in comparison with CP without HI (p=0.024, p=0.042, and p=0.017, respectively). **Conclusion:** Not only OS but also neuropsychological and psychosocial status are impaired by HI in long-term survivors of childhood-onset CP. HI is associated with severe obesity, reaching a plateau after >10 years of follow-up. Fatigue, reduced motivation and diarrhea have major negative impact on QoL of long-term CP survivors. As OS and PFS were not associated with the surgical degree of resection, gross-total resection should be avoided in case of HI for prevention of further hypothalamic damage in CP.

The authors have no relationships to disclose.

CRH/ACTH/CUSHING'S

P6

A Multi-Center Study of Follow-Up Intervals in Patients with Cushing's Disease

Eliza B. Geer[1], Ismat Shafiq[2], Murray B. Gordon[3], Alejandro Ayala[4], Vivien Bonert[5], Vijaya Surampudi[6], Laurence Katznelson[7], John D. Carmichael[5], Ekaterina Manuylova[2], Karen J. Pulaski-Liebert[8], Yelena Lalazar[1], Maureen P. Neary[9], William H. Ludlam[9], Dorothy Romanus[10], Dasha Cherepanov[10], Marianne Eagan[10], Jackie Lee[10], Michael S. Broder[10], Beverly MK Biller[8]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]University of Rochester Medical Center, Rochester, NY, USA; [3]Allegheny Neuroendocrinology Center, Allegheny General Hospital, Pittsburgh, PA, USA; [4]University of Miami and Jackson Memorial Hospital, Miami, FL, USA; [5]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [6]Harbor-UCLA Medical Center, Los Angeles, CA, USA; [7]Stanford University School of Medicine, Stanford, CA, USA; [8]Massachusetts General Hospital, Boston, MA, USA; [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [10]Partnership for Health Analytic Research, LLC, Beverly Hills, CA, USA

OBJECTIVES: Long-term follow-up of Cushing's disease (CD) is essential to diagnose recurrence and mitigate risks of increased morbidity/mortality. The frequency with which CD patients are followed in clinical practice is unknown. We determined proportions of CD patients seen at various intervals at 8 pituitary centers across the US. **METHODS:** Data on adult patients with newly diagnosed or recurrent CD were extracted starting at onset of symptoms in a retrospective chart review. We stratified patients by length of time since last visit: a) <1 year; b) 1-2 years; c) >2 years. We present descriptive interim analyses on the first 87 patients studied by the abstract deadline. **RESULTS:** 51 patients (59%) were last seen within the past 1 year, 16 (18%) within 1-2 years, and 20 (23%) were last seen >2 years prior. Evidence of transfer of care, with presumed follow-up elsewhere, was seen in 0% with a visit ≤1 year prior, 13% with last visit 1-2 years prior and 30% with last visit >2 years prior. Patients with last visit >2 years prior were older (median age: 50 vs. 47 years); female (95% vs. 69%); non-white (35% vs. 24%); had lower comorbidity burden (mean number of conditions: 3.3 vs. 4.5); and fewer had radiotherapy (10% vs. 20%) or pharmacotherapy (30% vs. 39%) for management of CD compared to those seen within 1 year. **CONCLUSIONS:** Many patients with CD went more than 1 year without a visit and are at risk of undetected recurrence or progression. A majority did not have documented transfer of care, but it is possible that some are being followed elsewhere. The possibility that demographics and adjunctive therapy may impact frequency of follow-up warrants further investigation. At study completion, a statistical analysis will be conducted to compare groups of patients based on length of time since last visit.

Beverly M.K. Biller receives honoraria from Cortendo and Novartis and research grants to her institution from Cortendo and Novartis; John Carmichael receives honoraria from Pfizer and Genentech and honoraria and research support from Novartis; Murray Gordon receives research grants from Novartis; Karen JP Liebert receives honorarium from Cortendo; William Ludlam and Maureen Neary receive salary and stock from Novartis Pharmaceuticals; Michael Broder, Dasha Cherepanov, Marianne Eagan, Jackie Lee, Dorothy Romanus are employees of Partnership for Health Analytic Research, LLC, a health services research company paid by Novartis to conduct this research. The other authors have no relationships to disclose.

P7

A Silent Corticotroph Pituitary Adenoma Evolving into Clinical Cushing's Disease

Dong-Hwa Lee[1], Min Kyeong Kim[1], A Ram Hong[1], Ji Won Yoon[2], Yong Hwy Kim[3], Jung Hee Kim[1], Sang Wan Kim[4], Chan Soo Shin[1], Seong Yeon Kim[1]

Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea[1], Department of Internal Medicine, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, Korea[2], Department of Neurosurgery, Seoul National University Hospital, Seoul, Korea[3], Department of Internal Medicine, Boramae Medical Center, Seoul, Korea[4]

A 53-year-old woman presented with a 2-month history of blurred vision in her left eye. Her serum cortisol and ACTH levels were elevated. She also had herpes zoster oticus in her right ear 3 months ago and developed diabetes mellitus recently.

She had been treated for a recurrent nonfunctional pituitary adenoma since 2004 with third transsphenoidal surgery (TSA) in 2011 and one gamma-knife surgery (GKS) in 2012. When she got last TSA in 2011, her serum cortisol level was not elevated but immunohistochemical features of pituitary tumor showed positive for ACTH and atypical pituitary adenomas.

Hence, further work-up for ectopic Cushing's syndrome or pituitary carcinoma was done. Serum and urine cortisol levels revealed a paradoxical response during high dose dexamethasone suppression test. Sellar magnetic resonance imaging showed a 1-cm sellar mass indicative of tumor recurrence. Nonetheless, we could not perform inferior petrosal sinus sampling because of left endophthalmitis. Positron emission tomography–computed tomography showed no lesions except the sellar mass. Hence, we diagnosed her with a silent corticotroph pituitary adenoma evolving into clinical Cushing's disease. She underwent second GKS. As bridge therapies due to severe hypercortisolism, we treated her with cabergoline and mitotane. She underwent diagnostic and therapeutic vitrectomy. She was diagnosed with Candida albicans endopthalmitis and treated with fluconazole. Her serum cortisol and ACTH levels decreased three months later.

The authors have no relationships to disclose.

P8

Body Composition in Pituitary, Adrenal and Iatrogenic Cushing's Syndrome and Effects of DHEAS Levels

Laura E. Dichtel[1], Miriam A. Bredella[2], Corey M. Gill[3], Ariana D. Riccio[4], Brian M. Russell[4], Karen K. Miller[1]

[1]Neuroendocrine Unit, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA; [2]Department of Radiology, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA; [3]Department of Radiology, Massachusetts General Hospital, Boston, MA, USA; [4]Neuroendocrine Unit, Massachusetts General Hospital, Boston, MA, USA

Hypercortisolemia is associated with abdominal adiposity and muscle wasting, as is hypoandrogenemia. Moreover, Cushing's disease has been shown to be associated with relative visceral adiposity. However, it is not known whether visceral adiposity is present in Cushing's syndrome of other etiologies or whether body composition is modulated by DHEAS levels, which vary widely depending on the etiology of Cushing's. We hypothesized that Cushing's syndrome would be associated with visceral adiposity and muscle wasting whether of pituitary, adrenal or iatrogenic origin, and that these body composition abnormalities would be attenuated in women with relatively higher DHEAS levels. We conducted a retrospective review of women with Cushing's of pituitary (N=25), adrenal (N=13) or iatrogenic (N=12) etiology and controls, matched 1:1 for BMI and age. Abdominal fat depots and psoas muscle mass were assessed from abdominal CT at L4. Urine free cortisol (UFC) equivalent was calculated from glucocorticoid doses for the iatrogenic Cushing's group. DHEAS levels were available for a subset of patients. Mean BMI was comparable among all groups. Mean age was higher in the iatrogenic than pituitary or adrenal groups. UFC was comparable in the pituitary, adrenal and iatrogenic groups (median 112, 108 and 134 mcg/24h, respectively). Visceral adipose tissue (VAT), VAT/subcutaneous adipose tissue (SAT), VAT/TAT and VAT/BMI were higher in the pituitary and adrenal Cushing's groups than controls. There was a trend toward higher VAT in pituitary versus iatrogenic Cushing's when controlling for age (p=0.06). When age, BMI, Cushing's etiology, UFC and DHEAS were entered into multivariate models, DHEAS was an independent negative determinant of TAT, VAT, VAT/SAT, and an independent positive determinant of muscle mass. In conclusion, hypercortisolemia is associated with visceral adiposity in Cushing's of pituitary and adrenal etiology. Higher DHEAS levels may confer relative protection from abdominal fat accumulation and muscle wasting in women with Cushing's syndrome.

The authors have no relationships to disclose.

P9

Comparison of Corticotropin Releasing Hormone and Desmopressin as Stimulators in Inferior Petrosal Sinus Sampling

Cheol Ryong Ku[1], Sun Ho Kim[2], Eun Jig Lee[1]

Endocrinology[1] and Neurosurgery[2], Yonsei University College of Medicine, Seoul, Republic of Korea

Objective: Inferior petrosal sinus sampling (IPSS) is a very useful test to differentiate the Cushing's disease from ectopic ACTH secreting neuroendocrine tumor. Although corticotropin releasing (CRH) is widely used stimulator during IPSS in patients with ACTH dependent Cushing syndrome, it is frequently unavailable due to the matter of manufacturer and expensive. In this study, we compared the stimulatory effects of desmopressin with those of CRH during IPSS. **Method:** Basal ACTH level and post-stimulatory ACTH level during 15 min after CRH or desmopressin injection were analyzed. During IPSS, each ACTH was collected from peripheral, both interpetrosal, and both jugular venous sampling. Thirty six patients with Cushing's disease and 4 patients with simple obesity participated in this study. **Result:** Among 36 patients with Cushing's disease, stimulators during IPSS were injected in 27 patients with CRH and 9 subjects with desmopressin. There were no differences in age, sex, tumor size, basal ACTH, and 24hr urine cortisol between patients with each stimulatory agent. During IPSS, each stimulator showed the similar results in peak IPS ACTH level (1653 pg/mL; 821~2435 pg/mL vs. 1862 pg/mL; 1621~8571 pg/mL; median; interquartile range), IPS : peripheral ratio (19.5; 11.2~34.8 vs. 33.7; 20.5~58.6; median; interquartile range), and normalized ACTH/prolactin IPS : peripheral ratio (5.8; 8.2~10.8 vs. 19.8; 6.5~24.8; median; interquartile range). Furthermore, patients with simple obesity showed the similar IPS : peripheral ratio and normalized ACTH/prolactin IPS : peripheral ratiowith those of Cushing's disease. In tumor localization, MRI showed the more accurate predictive value than IPSS (86.7% vs. 58.3%; P=0.037, respectively). However, there was no difference between each stimulator in prediction for tumor localization (75.0% and 50.0% in CRH and desmopressin, respectively). **Conclusion:** Desmopressin showed the similar stimulatory effect compared with CRH. Further analysis should be needed with larger number of patients to evaluate the effects of desmopressin in IPSS.

The authors have no relationships to disclose.

P10

Cushing's Disease and Co-existing Pheochromocytoma

Philip C Johnston, Pablo Recinos, Richard Shewbridge, Laurence Kennedy, Amir H. Hamrahian

Department of Endocrinology, Diabetes and Metabolism, and Department of Neurosurgery Cleveland Clinic Foundation, Cleveland, Ohio, USA

We report a 46 year old female who presented with a one year history of bruising, thin skin and weight gain. In addition; she reported flushing of her chest, heat intolerance, palpitations and abdominal pain. On clinical examination she appeared cushingoid, blood pressure was elevated at 160/98 mmHg.

Biochemical investigations indicated ACTH-dependent Cushing syndrome: 24 hr UFC 300 µg (0-50), ACTH 119 pg/ml (8-42); midnight salivary cortisol 950 ng/dL (<100). MRI pituitary demonstrated a sellar lesion; 14x9x9 mm suggestive of a pituitary macroadenoma. To investigate the symptoms of flushing and palpitations, plasma fractionated catecholamines and metanephrines were performed and were elevated; norepinephrine 822 pg/mL (80-520), epinephrine < 10 pg/ml (10-200), dopamine <20 pg/ml (0-20), normetanephrine 1250 pg/ml (18-101), metanephrine 34 pg/ml (12-67). CT abdomen revealed a lipid poor right adrenal mass measuring 17 x 36 mm with Hounsfield units of 47, consistent with a pheochromocytoma.

The patient started phenoxybenzamine and subsequently uptitrated the dose for three weeks prior to elective adrenalectomy. A robotic right trans-abdominal lateral adrenalectomy was performed without complications, histology confirmed a pheochromocytoma. One month post-adrenalectomy plasma fractionated catecholamines and metanephrines were normal. The patient continued to be hypercortisolemic post-op. Six weeks after adrenal surgery transsphenoidal resection of the pituitary mass was performed, the histology revealed an adenoma which was diffusely positive for ACTH, it did not stain with any other anterior pituitary hormones. At 3 months post-pituitary surgery, she had normal plasma metanephrines and 24 hr UFC levels with no visible residual disease on pituitary MRI.

Pheochromocytoma is associated with excess morbidity and mortality if undiagnosed, it was therefore fortuitous that this diagnosis was made prior to pituitary surgery. Clinicians should be alert to the about rare association of pheochromocytoma in patients with clinically significant pituitary adenomas, and pursue further work up if clinically indicated.

Breckenridge SM, Hamrahian AH, Faiman C, Suh J, Prayson R, Mayberg M. Coexistence of a pituitary macroadenoma and pheochromocytoma. A case report and review of the literature. Pituitary 2003 6(4):221-225

The authors have no relationships to disclose.

P11

Disease Characteristics Associated with Cushing's Disease: A Multi-Center US Study

Ismat Shafiq[1], Eliza B. Geer[2], Murray B. Gordon[3], Alejandro Ayala[4], Vivien Bonert[5], Vijaya Surampudi[6], Laurence Katznelson[7], John D. Carmichael[5], Ekaterina Manuylova[1], Karen J. Pulaski-Liebert[8], Yelena Lalazar[2], Maureen P. Neary[9], William H. Ludlam[9], Dasha Cherepanov[10], Marianne Eagan[10], Jackie Lee[10], Michael S. Broder[10], Beverly MK Biller[8]

[1]University of Rochester School of Medicine and Dentistry, Rochester, NY, USA; [2]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [3]Allegheny Neuroendocrinology Center, Allegheny General Hospital, Pittsburgh, PA, USA; [4]University of Miami and Jackson Memorial Hospital, Miami, FL, USA; [5]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [6]Harbor-UCLA Medical Center, Los Angeles, CA, USA; [7]Stanford University School of Medicine, Stanford, CA, USA; [8]Massachusetts General Hospital, Boston, MA, USA; [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [10]Partnership for Health Analytic Research, LLC, Beverly Hills, CA, USA

OBJECTIVES: Cushing's disease (CD) is a rare disorder resulting from excessive exposure to glucocorticoids, caused by an adrenocorticotropic hormone secreting pituitary tumor. Our aim was to describe the natural history and comorbidities for CD patients in the US, comparing results with a European registry, ERCUSYN (Valassi Eur J Endocrinol 2011). **METHODS:** Retrospective data were collected from patients' medical records at 8 US pituitary centers. Eligible patients were diagnosed within the past 20 years and had age ≥18 years at diagnosis. Data included demographics, comorbidities, and treatment. Interim findings are presented; final results will be shown at the meeting. **RESULTS:** The interim analysis included 87 patients with a median age of 39 years at diagnosis (range: 18-78); 70.1% were white; 6.9% were African American; 75.9% were female. At presentation, most common symptoms were weight gain (62.1%), fatigue (52.9%), muscle weakness (51.7%), easy bruising (49.4%), unwanted hair growth (35.6%), headache (33.3%), anxiety (28.7%) and stretch marks (26.4%). The most commonly noted signs were striae (48.3%), posterior cervical and supraclavicular fat pads (48.3%; 42.5%), facial plethora and rounding (46%; 41.4%), central obesity (36.8%) and hirsutism (28.7%). First-line treatment was pituitary surgery in 96.6%. 13.8% had radiotherapy, 29.9% had pharmacotherapy, and 6.9% had adrenalectomy sometime during their care. Commonly observed comorbid conditions were hypertension (69%), hyperlipidemia (49.4%), type 2 diabetes (29.9%), obesity (28.7%), depression (26.4%) and anxiety (23%). The most commonly identified disease characteristics in our study were hypertension, weight gain, fatigue, and muscle weakness, and those in the European study were weight gain (82%), hypertension (76%), skin alterations (78%), and myopathy (67%). **CONCLUSIONS:** This sample is comparable in demographic characteristics and clinical features to ERCUSYN, except for our inclusion of race/ethnicity and slightly different frequencies of common disease characteristics (fatigue and anxiety were noted only in US study). Our results underscore the substantial comorbidity burden with CD.

John Carmichael receives honoraria from Genentech and Pfizer, and honorarium and research support from Novartis; William Ludlam and Maureen Neary receive salary and stock from Novartis Pharmaceuticals; Karen JP Pulaski-Liebert receives honorarium from Cortendo; Beverly MK Biller receives honoraria from Cortendo and Novartis and research grants to her institution from Cortendo and Novartis; Murray Gordon receives research support from Novartis; Michael Broder, Dasha Cherepanov, Marianne Eagen, and Jackie Lee are employees of Partnership for Health Analytic Research, LLC, a health services research company paid by Novartis to conduct this research.

The other authors have no relationships to disclose.

P12

Efficacy and Safety of Retinoic Acid in Patients with Cushing's Disease: Results of a Prospective Study

Lucio Vilar[1,2], José Luciano Albuquerque[1], Patricia S. Gadelha[1], Frederico Rangel Filho[1], Ruy Lyra[1]

[1]Division of Endocrinology, Hospital das Clinicas, Federal University of Pernambuco, Recife, Brazil, [2]Diabetes & Endocrinology Center of Pernambuco, Recife, Brazil

Objective: To evaluate the efficacy and safety profile of retinoic acid treatment in patients with Cushing's disease (CD) after a failed transsphenoidal surgery. **Methods:** This is a prospective open trial. Fifteen patients with CD (9 men and 6 postmenopausal women) unsuccessfully treated by transsphenoidal surgery were given retinoic acid for 6–12 months. The drug was started on 20 mg daily and the dosage was increased up to 80 mg daily if needed and tolerated. ACTH, 24 h urinary free cortisol (UFC), and midnight salivary cortisol (MnSaC) as well as clinical features of hypercortisolism and possible side effects of retinoic acid, were evaluated at baseline and monthly during retinoic acid administration. **Results:** Normalization of UFC and MnSaC levels occurred in 6 patients (40%) at doses ranging from 40 to 80 mg daily (mean 63.3 ± 15.05; median, 60), whereas reductions ranging from 14.3 to 50.3% were found in the remaining. Although ACTH levels decreased in all patients, normalization was only achieved in 1 out of 5 patients (20%) whose baseline values were above the upper limit of normal. Responsive patients had significantly lower UFC and MnSaC levels but there were overlapping values in both groups. Blood pressure, glycemia, and signs of hypercortisolism improved, to a variable extent, during treatment. Retinoic acid was well tolerated and mild and transitory side-effects, particularly artrhalgias and xerophthalmia, were reported by 5 patients (30%). Mild and transient elevation of serum transaminases were found in 2 patients (13.3%). No significant change in kidney function tests or in the lipid profile was depicted. **Conclusions:** Our results suggest that retinoic acid may be an effective and safe therapy for CD patients with persistent hypercortisolism, particularly those with lower UFC and MnSaC levels.

The authors have no relationships to disclose.

P13

Expanded Endonasal Endoscopic Approach for Selective Adenomectomy in Cushing's Disease: 7-Year Experience of a Single Surgical Team

Gary L. Gallia[1], Adela Wu[1], Roberto Salvatori[2], Gary Wand[2], Krysta Bearish[1], Ari M. Blitz[3], Douglas D. Reh[4], and Masaru Ishii[4]

[1]Department of Neurosurgery, [2]Division of Endocrinology, Department of Medicine, [3]Division of Neuroradiology, Department of Radiology, [4]Department of Otolaryngology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Objective: Surgery remains the treatment of choice in Cushing's disease when cure is possible. Here we report our experience using an expanded endonasal endoscopic approach for selective tumor resection in patients with Cushing's disease. **Methods:** The medical records of patients with Cushing's disease who underwent an expanded endonasal endoscopic approach for selective adenomectomy by a single surgical team were reviewed. Remission was defined by postoperative serum cortisol levels less than 5 mcg/dl or normal follow-up 24-hour urine free cortisol levels. Length of follow-up was calculated based on the last endocrinological evaluation. **Results:** Between January 2008 and December 2014, 37 consecutive patients with Cushing's disease treated by a single neurosurgeon and one of two otolaryngologists were identified. The average age of patients in this series was 44 years (median: 41 years; range: 16-75 years). Ninety-two percent of patients were female and 81% were of Caucasian descent. In this series, 35 patients (95%) presented with newly diagnosed Cushing's disease. On MR imaging, 17 patients (46%) had microadenomas, 17 (46%) had macroadenomas, and 3 (8%) had negative MR scans. Before surgery, 5 patients (14%) underwent inferior petrosal sinus sampling. Thirty-four (92%) patients underwent a single procedure; three patients underwent a second endoscopic surgery (4, 7, and 10 days after the initial procedure) for postoperative hypercortisolemia. Thirty-two patients (86%) had a cortisol nadir less than 5 mcg/dl prior to hospital discharge. Four patients (11%) had transient diabetes insipidus and 2 patients (5%) had transient delayed syndrome of inappropriate antidiuretic hormone secretion. There were no new permanent endocrinopathies. Postoperative complications occurred in 6 patients (17%) including one patient who developed a CSF leak, which was eventually treated with a VP shunt due to elevated intracranial hypertension. A second patient developed epistaxis, which was managed conservatively. Four patients developed postoperative deep venous thrombosis and/or pulmonary embolism. Thirty-three patients (89%) remain in remission with an average follow-up of 561 days (median: 383 days; range: 10-2294 days). One patient recurred 17 months after surgery and hypercortisolemia persisted after surgery in three patients: one with a negative MR scan and 2 with extension of tumor outside of the sella. **Conclusion:** Expanded endonasal endoscopic approaches for selective adenomectomy result in high remission rates and low endocrinological and surgical complication rates in patients with ACTH-secreting pituitary adenomas.

Ari Blitz receives honorarium from Siemens. The other authors have no relationships to disclose.

P14

Experience of Bilateral Inferior Petrosal Sinus Sampling with DDAVP Stimulation Test in the Diagnosis of 275 Cases with the Cushing's Syndrome in a Single Center

[1]Lin Lu, [2]Yong Yao, [3]Xiaobo Zhang, [1]Zhaolin Lu, [2]Renzhi Wang, [1]Feng Gu

[1]Department of Endocrinology, [2]Department of Neurosurgery, [3]Department of Radiology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese academy of Medical Science. National Key Program of Clinical Science (WBYZ2011-873)

Objective: The inferior petrosal sinus sampling (IPSS) with CRH stimulation has been widely used as gold standard to differentiate the source of ACTH in Cushing's syndrome. This study is to analyze the efficacy of IPSS in the basal and after desmopressin (DDAVP) stimulation state in the diagnostic evaluation in Chinese patients of Cushing's syndrome. **Method:** Since the CRH was not available in China, IPSS with DDAVP stimulation test has been developed from 2010. IPSS technique has been carried out in ACTH dependent Cushing syndrome cases whom the source of ACTH secretion couldn't be identified clearly with Sella MRI technique, Chest CT and/or dynamic endocrine tests. The sensitivity was calculated on the basis of endocrinological evaluation and pathological confirmation by the recovery from Cushing's syndrome after surgical intervention. As a result of IPSS, pituitary-dependent Cushing's disease was diagnosed with a baseline central to peripheral ACTH ratio of >2.0 or with a ratio of >3.0 after DDAVP stimulation. **Results:** Data of 275 admitted cases with Cushing syndrome have been collected to identify the accuracy of this test in the diagnosis in the Cushing' syndrome. There were 269 patients with ACTH-producing pituitary adenoma and 6 patients with ectopic ACTH/CRH syndrome in this series. The correct catheterization rate was 100%. IPSS with baseline ACTH assay and IPSS with DDAVP stimulation test had sensitivity of 85.6% and 99.2% respectively. In addition, the bilateral jugular vein sampling were also evaluated and proved no significant diagnostic accuracy. The efficacy (40.3%) of localization was quite low in this series. Few complications were found after this procedure. **Conclusion:** IPSS with DDAVP stimulation test have been developed as a key and experienced procedure in the diagnosis of Cushing syndrome in our center. The DDAVP stimulation test in the IPSS procedure had similar efficacy to CRH stimulation test.

The authors have no relationships to disclose.

P15

Prolonged Adjuvant Temozolomide Treatment in a Case of Aggressive ACTH-secreting Pituitary Adenoma

D. Iacovazzo[1], S. Chiloiro[1], S. Piacentini[1], F. Lugli[1], A. Giampietro[1], M. Balducci[2], F. Doglietto[5], G. Maira[3], L. Lauriola[4], A. Bianchi[1], L. De Marinis[1]

[1]Endocrinology, [2]Radiotherapy, [3]Neurosurgery, [4]Pathology, Università Cattolica del Sacro Cuore, Policlinico A. Gemelli, Rome, Italy; [5]Neurosurgery, University of Brescia, Brescia, Italy

Temozolomide has proved efficacy for the management of aggressive pituitary adenomas and pituitary carcinomas. Treatment timing and duration of treatment are not standardized, and acquired resistance at re-treatment seems a frequent event. No data are available regarding the outcome and tolerability of long-term treatment. Here we report the case of an aggressive ACTH-secreting pituitary adenoma successfully controlled with prolonged adjuvant temozolomide treatment.

A now 80-year-old female patient was referred to our Pituitary Unit in 2004 after the partial resection of a non-functioning pituitary adenoma. Histological examination showed a pituitary adenoma with positive immunohistochemistry for ACTH, PRL, GH and low proliferation index (Ki-67<1%). Over the following years a slight progression of residual disease was observed. In 2011 the patient presented with progressive signs and symptoms of hypercortisolism; biochemistry was consistent with Cushing's disease. A trial of pasireotide treatment was attempted but was not effective in controlling the disease. The residual tumor significantly progressed and the patient underwent partial resection of the pituitary lesion. Pathology showed an atypical pituitary adenoma with positive staining for ACTH and a Ki-67 of 5%. Conventional radiation treatment was administered together with adjuvant concomitant temozolomide treatment, which was then resumed at the dosage of 150 mg/m2 for 5 consecutive days every month. The treatment resulted in the complete remission of Cushing's disease and in partial response and consequent stabilization of the tumor. The treatment is still ongoing after 24 months without significant adverse events.

In conclusion, adjuvant temozolomide treatment is an effective and well-tolerated treatment for aggressive pituitary neoplasms. Prolonged treatment might control the disease without significant toxicity.

The authors have no relationships to disclose.

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

P16

Succesful Treatment with Somatostatin and Dopamine Analogues in a Patient with Nelson's Syndrome

Tkatch Julieta, Lopez Florencia, Guitelman Mirtha Adriana

Endocrinology Division, Hospital Carlos G Durand, Buenos Aires, Argentina

Introduction: Nelson's syndrome (NS) is a potential severe complication of bilateral adrenalectomy performed in the treatment of cushing's disease (CD). Management of Nelson's syndrome largely consists of surgery and/or radiotherapy because there are limited medical therapy options. Treatment with the somatostatin analog octreotide has yielded variable to no benefit; no data with cabergoline alone or combined with somatostatin analogs. **Objective:** The successful response of octreotide combined with cabergoline in a patient with NS. **Case report:** A 33 year-old female was diagnosed with CD in 2007 at age 26, and underwent transphenoidal surgery of a pituitary macroadenoma that year. She persisted with active disease and a partial empty sella with no further image at the MRI. During the following 3 years she received medical treatment with slight improvement. In 2010 she underwent radiosurgery, and bilateral adrenalectomy 1 year later. She subsequently developed Nelson's syndrome. Hyperpigmentation, ACTH 4312 pg/ml (10-70 pg/ml), and parasellar and supraselar tumor expansion were the initial presentation. Computerized visual field was normal. She began octreotide long-acting release 30 mg/28 days im, together with cabergoline 1 mg/week orally. After 18 months therapy, ACTH declined to 1236 pg/ml, and MRI showed 80% tumor reduction. Hyperpigmentation progressively improved. **Conclusion:** A case of Nelson's syndrome with significant clinical, biochemical and image responses to octreotide plus cabergoline administration is reported. This result may be related to the up regulated SSTR2 in ACTH tumors in NS, and the known expression of D2R, that might have an enhancer effect.

Mirtha Guitelman is a speaker for Novartis and Sanofi Aventis. The other authors have no relationships to disclose.

P17

The Establishment and Use of Database of Cushing's Disease

Ming Feng, Yong Yao, Kan Deng, Bowen Sun, Renzhi Wang

Department of Neurosurgery, Peking Union Medical College Hospital, Peking, China

Objective: We establish a database of Cushing's disease (DCD) to preserve all the clinical information, including record, MRI, pathology and surgical material. **Methods:** We use Caché software to set up a database of Cushing's disease. The DCD can grab data automatically from HIS (hospital information system), LIS (laboratory information system) and RIS (radiology information system). In addition, the DCD can capture the surgical and pathological data from HIS. Electronic forms of for outpatients were also made to preserve the information post operation. And the DCD can remind the doctors to follow-up in time. **Results:** From the year 2012 to 2014, 319 cases of Cushing's disease patients were involved in DCD. In DCD, there are 223 females and 106 males, 255 micro-adenoma and 99 macro-adenoma, 60 recurrent cases. **Conclusion:** DCD can preserve all the clinical information of Cushing's disease in inpatient and outpatient. Prospective and multiple center clinical study can perform using the database.

The authors have no relationships to disclose.

GENETICS

P18

Differential Expression of MicroRNAs in GH-secreting Pituitary Adenomas with Responsiveness to Somatostatin Analogs

Zhi-Gang Mao[1], Dong-Sheng He[1], Jing Zhou[2], Bin Yao[3], and Hai-Jun Wang[1]

[1]Department of Neurosurgery and Pituitary Tumor Center, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [2]Department of Histology and Embryology, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China; [3]Department of Endocrinology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: The purpose of this study was to (1) identify specific miRNAs in growth hormones (GH)-secreting pituitary adenomas; (2) determine the relationship between the expression of these miRNAs and tumor size, somatostatin analogs treatment, and responsiveness to somatostatin analogs (SSA).

Methods: Fifteen GH-secreting adenomas patients were treated with lanreotide for 4 months before surgery. Patients with 50% reduction of GH secretion by lanreotide were considered as SSA responders, while patients with less than 50% of GH reduction were considered as SSA nonresponders. We analyzed the miRNAs in 21 GH-secreting pituitary adenomas and 6 normal pituitaries by miRCURY™ LNA array and some differentially expressed miRNAs were validated by quantitative real-time PCR.

Results: Fifty-two miRNAs were differentially expressed between GH-secreting pituitary adenomas and normal pituitaries. Differential expression of 9 miRNAs was observed between micro- and macro-adenomas. Thirteen miRNAs were differentially expressed between tumor samples from lanreotide-treated patients and those from lanreotide-untreated patients. Seven miRNAs were differentially expressed between SSA responders or GH nonresponders. Several identified miRNAs may be involved in cell proliferation, apoptosis, cancer development and progression.

Conclusions: Our results indicate that altered miRNAs expression is involved in GH-secreting pituitary adenomas transformation, which will shed light on the mechanisms for the treatment of acromegaly by SSA. Identification and characterization of the targets of altered miRNAs genes may elucidate molecular mechanisms involved in the pathogenesis of pituitary adenoma.

The authors have no relationships to disclose.

P19

Influence of Dopamine Receptor Subtype 2 and Somatostatin Receptor Subtypes 2 and 5 Polymorphisms in Response to Treatment in Pituitary Adenomas

Bueno CBF[1,2], Trarbach EB[2], Jallad RS[1,2], Duarte FHG[1], Machado MC[1,2], Caccelli M[1], Fragoso MCBV[1], Bronstein MD[1,2], Glezer A[1,2]

[1]Unidade de Neuroendocrinologia, Disciplina de Endocrinologia e Metabologia, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, HC-FMUSP, São Paulo, Brasil; [2]Laboratório de Endocrinologia Celular e Molecular LIM/25, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, HC-FMUSP, São Paulo, Brasil

Pituitary adenomas express dopamine and somatostatin receptors and can be medically treated with dopamine agonists (DA) and/or somatostatin receptor ligands (SRL). It was suggested that polymorphisms (SNPs) in genes encoding dopamine 2 receptor (D2R) and somatostatin receptors 2 and 5 (SSTR2 and 5) could be associated with variable effectiveness of DA and SA treatment.

In order to study the potential influence of D2R and/or SSTR2/SSTR5 SNPs on the response to treatment with DA and/or SA, we evaluated D2R SNPs (rs1079597, rs1076560, rs1800497 and rs6275) in 198 patients with pituitary tumors on DA (146 prolactinomas,26 somatotrophinomas and 26 corticotrophinomas) and SSTR2 (rs998571 and rs1466113) and SSTR5 SNPs (rs3751830, rs4988487, rs169068, rs34037914, rs642249) in 51 acromegalic patients on SRL. In addition, 71 patients with acromegaly on DA/SRL association treatment were genotyped for D2R, SSTR2 and SSTR5 SNPs. All polymorphisms were assessed by real time PCR genotyping (TaqMan assay).

In patients with prolactinoma, DR2 rs1079597 allele C or DR2 rs1800497 allele G were related to bromocriptine response (P= 0.009 and P=0.031), whereas patients with DR2 rs6275 allele A or rs1799732 allele ins C showed higher sensitivity to cabergoline (P=0.012 and P=0.014). Other authors had already described that rs6275 allele T was more frequent in resistant prolactinomas (Filopanti, 2008). Also, the presence of functional SNP rs1801028 allele C was associated to tumor shrinkage during treatment with cabergoline (P=0.048). Regarding corticotrophinomas, none D2R SNPs showed significant association with the response to DA. In acromegaly, we found an association between SSTR2 rs1466113 allele G and normalization of GH after combined treatment with SRL and cabergoline (P=0.020). However, previous results correlated only with the presence of SSTR5 variants with reduction of GH and IGF1 after SRL treatment (Ciganoka, 2011). In conclusion, our data point to an influence of D2R and SSTR SNPs on the therapeutic response to DA and SRL in pituitary tumors.

The authors have no relationships to disclose.

P20

The Prevalence of Multiple Endocrine Neoplasia-1 (MEN-1) in Acromegaly: Phenotype/Genotype Correlation

Babak Torabi Sagvand[1], Shafaq Khairi[1], Brooke Swearingen[2], Anne Klibanski[1], Lisa Nachtigall[1]

[1]Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, [2]Department of Neurosurgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Pituitary adenomas occur in up to 40% of patients with MEN-1, 10% of which are somatotropinomas. MEN-1 is reported in 3% of patients with pituitary adenomas, but limited data confirm this.

The goal of this study was to evaluate the prevalence of MEN-1 in patients with acromegaly and determine if known MEN-1 mutations were associated. The records of 198 consecutive patients with acromegaly evaluated at our Center were reviewed. Twelve (6.06%) with MEN-1 were identified by one of the following: two or more MEN1-associated endocrine tumors, one MEN1-associated tumors and a first degree relative with MEN-1, or genetically proven MEN-1. Commercially available genetic testing for MEN-1 was performed in 9 consenting patients and tested for known MEN-1 mutations.

Of these 12 patients (7F/5M), 11 had primary hyperparathyroidism; two had a neuroendocrine pancreatic tumor in addition to acromegaly. The mean age at diagnosis of acromegaly was 46.5±16 years. Four (33.3%) had family history of MEN-1 in a first degree relative. The mean random GH and IGF-1 index at the time of diagnosis of acromegaly was 9.6±7.1 ng/dl and 2.49±0.9 (x upper normal range), respectively. In 9 patients tested for known MEN-1 mutations all were negative. Seven (58.3%) had at least one cancer (4 with thyroid, one breast, one prostate and one cervical) compared to 14% cancer incidence in patients with acromegaly without MEN-1 (p <.0001).

The prevalence of MEN-1 in patients with acromegaly was 6%, twice that previously reported in pituitary tumor series. Although negative genetic tests may be expected in up to 15% of MEN-1, the negative findings in all tested patients suggest that other mutations may explain the association of the MEN-1 phenotype in acromegaly. Furthermore, the phenotype of clinical MEN-1 in acromegaly may be associated with an increased risk of other malignancies.

Anne Klibanski receives grant support from Ipsen, Novartis and Rhythm Pharmaceuticals. The other authors have no relationships to disclose.

GROWTH HORMONE/ACROMEGALY

P21

Analysis of Factors Influencing Short-term Effect of Presurgical Pharmacological Therapy and Transsphenoidal Microsurgery for Somatotropinomas

Chen Xi, Chan Juan, Xu Yu, Hu Hang, Li Chaoxi, Zhang Huaqiu, Lei Ting*

Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Objective: The aim of this study was to analyze factors influencing short-term effect of presurgical pharmacological therapy and transsphenoidal microsurgery for Somatotropinomas. **Methods:** The clinical data of 53 patients underwent presurgical pharmacological therapy and transsphenoidal microsurgery for somatotropinomas were retrospectively analyzed. These patient series were classified according to sex, neuropathological evaluation, tumor size and the presence of invasion etc., and then analyzed factors influencing short-term effect of presurgical pharmacological therapy and transsphenoidal microsurgery for Somatotropinomas. **Results:** Serum GH levels decreased by >50% from baseline in 62.26% of patients receiving presurgical pharmacological therapy. Statistical analysis of the data concerning the influence of sex, neuropathological evaluation, tumour size, the presence of invasion on short-term presurgical pharmacological therapy effect was performed using a chi-squared test, no significant correlation (P>0.05) was found among these factors and short-term presurgical pharmacological therapy effect in our series. Total remission rate was 43.40%, Statistical analysis of the data concerning the influence of sex, neuropathological evaluation, tumour size, the presence of invasion, and short-term presurgical pharmacological therapy effect on remission rate was performed using a chi-squared test, a significant correlation (P<0.05) was found among tumour size, presence of invasion, short-term presurgical pharmacological therapy effect and remission rate, while no significant correlation (P>0.05) was found among sex, neuropathological evaluation and remission rate in our series. **Conclusion:** Short-term presurgical pharmacological therapy effect revealed no significant correlation with sex, neuropathological evaluation, tumour size or the presence of invasion. Total remission rate correlated with the tumour size, presence of invasion and short-term presurgical pharmacological therapy effect.

The authors have no relationships to disclose.

P22

Body Image Disturbance in Pituitary Patients: Acromegaly Compared with Non-functioning Pituitary Adenomas and Controls

Helen M Conaglen[1], Dennis de Jong[2], John V Conaglen[1,3], Marianne S Elston[1,3]

[1]University of Auckland, Waikato Clinical Campus, Hamilton, New Zealand; [2]University of Waikato; [3]Department of Endocrinology, Waikato Hospital, Hamilton, New Zealand

Background: Excess GH in acromegaly alters physical appearance and function, and affects quality of life (QoL). Non-functioning pituitary adenomas (NFPA) may cause pituitary hormone dysfunction without altering appearance, making comparisons feasible. Body image (BI) is a construct assessed in terms of a person's dissatisfaction, dysphoria, ideals, and BI disturbance. One case report described BI affected by acromegaly, but no studies have assessed BI disturbance in acromegaly. **Aim:** To evaluate BI disturbance in acromegaly, NFPA patients and controls. **Method:** The cross-sectional survey was conducted in acromegaly patients, age-matched NFPA patients and controls recruited from family or friends of patients. Participants completed the Duke Health Profile, Body Image Disturbance Questionnaire (BIDQ), and Hospital Anxiety & Depression Scale (HADS). **Results:** Thirty-one acromegaly and 29 NFPA patients, and 21 control participants completed the study. BMIs raged between 18.9 and 61.7 with 1/3 of the control group and ~1/2 of each patient group being obese. BI concerns were expressed by 63% of females and 27% of males studied distributed across all groups. Acromegaly and NFPA patients returned worse physical health scores (p<.0001 &.01 respectively), and perceived health was lower in acromegaly patients than the Duke reference group (p<.05). Self-esteem was lower in obese participants regardless of group. Obese acromegaly patients recorded significantly lower QoL relating to appearance, than their non-obese counterparts (p<.05). 75% of those with anxiety or depression problems were acromegaly patients, but group comparisons showed no significant differences in HADS scores. **Conclusion:** The primary hypothesis, that there would be more likelihood of BI disturbance in acromegaly patients because of the physical changes in acromegaly, was not supported by the data, with no significant differences being found between groups with respect to BI disturbance. Differences were found in obese patients with acromegaly, with psychological and personal relationship issues more problematic for these patients.

The authors have no relationships to disclose.

P23

Can Growth Hormone (GH) Replacement Therapy Improve Renal Function in Patients with GH Deficiency?

Yuki Kasamo[1, 2], Shingo Fujio[2], Mika Habu[2], Syunji Yunoue[2], Hirofumi Hirano[2], Manoj Bohara[2], Kazunori Arita[2]

[1]Department of Neurosurgery, Imamura Bun-in Hospital, Kagoshima, Japan, [2]Department of Neurosurgery, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan

Introduction: Growth Hormone (GH) is well known to increase glomerular filtration rate (GFR). However, it is not yet clear if GH replacement therapy can improve renal function in patients with GH deficiency. We investigated the changes of estimated GFR (eGFR) and IGF-1 in the patients with GH deficiency undergoing GH replacement therapy. Materials and **Methods:** From September 2006 to January 2013, there were 37 patients who were diagnosed with adult GH deficiency and had GH replacement therapy. Of these, 31 patients (18 male and 13 female, mean age 49.1 ± 14.5 years) continued GH replacement therapy for more than two years. IGF-1, serum creatinine, and body composition were evaluated before and after 3 months, 1 year and 2 years of GH replacement. To calculate eGFR, Japanese Society of Nephrology calculation method was used, which based on age, gender and serum creatinine. **Results:** 2-year GH replacement therapy improved IGF-1 SD score significantly from -2.68 ± 1.66 to -0.70 ± 1.56 ($p<0.001$). eGFR did not improve significantly (from 82.8 ± 26.5 to 80.6 ± 19.7 ml/min/1.73m3), but the patients with low eGFR tended to have increased eGFR after treatment (Patients with eGFR < 90; from 69.5 ± 16.2 to 72.1 ± 15.5 ml/min/1.73m3). In body composition, lean body mass increased significantly from 45.1 ± 9.6 kg to 46.4 ± 8.8 kg ($p=0.02$). Muscle mass and body water mass tended to increase, and fat mass tended to decrease. **Conclusion:** eGFR did not improve significantly after GH replacement therapy. GH replacement therapy might increase body muscle. There was a possibility that increased body muscle elevated serum creatinine, and affected eGFR values apparently.

The authors have no relationships to disclose.

P24

Combined Treatment with Octreotide LAR and Pegvisomant in Patients with Gigantism-acromegaly

Mangupli Ruth, Camperos Paul, Cuauro Elvia, Luna Magda

Neuroendocrinology Section, Department of Neurosurgery, Hospital Universitario, Caracas, Venezuela

Gigantism due to pituitary growth hormones excess before epiphyseal closure is a rare condition. We studied eight giant patients with GH secreting macroadenomas and evaluated clinical, biochemical and tumor size in response to combined treatment with octreotide LAR and pegvisomant. **Subjects and Methods:** Eight giant patients were studied in a single center at a university hospital (six males, two females) who developed their disease before 21 years of age. Median age at diagnosis was 18.7 (range 12-28). All patients presented with accelerated growth and height above the 95th centile. They were incompletely controlled by surgery, radiotherapy or somatostatin analogs. **Results:** Median stature at diagnosis was 192 cm, range (178-218 cm). Mean basal GH concentration was 34.9 ug/L and mean IGF-1 885.4 ng/mL. Four patients presented with moderate hyperprolactinemia.MRI of the sellar region revealed a macroadenoma in all patient. Transsphenoidal surgery was performed in one patient and transcranial approach followed by radiotherapy in another patient. Six patients were treated with octreotide as primary therapy resulting in tumor shrinkage in 4/6 (64%) but IGF-1 levels remained high. In all cases 20 mg/day pegvisomant was added without discontinued the somatostatin analog. Administration of combined octreotide LAR (20 mg every month) and pegvisomant (20 mg every day) therapy resulted in normalization of IGF-1, clinical improvement and cessation of somatic growth without changes in tumor volume. **Conclusions:** Young patients have bigger and more aggressive tumors. Nor surgery neither radiotherapy or somatostatin were effective to normalize hormonal values or improve clinical symptoms. The incidence of cosecretion of prolactin with GH and hyperprolactinemia was higher than that in adults. Considering the long-term sequela the management of pituitary GH secreting adenomas in giant patients may require a multiple therapeutic approach. Our experience indicates that combination therapy with a long acting somatostatin analog and pegvisomant was successful in the treatment of gigantism- acromegaly.

The authors have no relationships to disclose.

P25

Effect of Treatment with Pegvisomant on Bone Mineral Density and Bone Markers in Patients with Acromegaly

Adriana P. Kuker[1], Juliana Bicca[2], Carlos Reyes-Vidal[1], Jean Carlos Fernandez[1], Elizabeth Shane[1], Pamela U. Freda[1], Jose Bento[2]

[1]Department of Medicine, Division of Endocrinology, Columbia University College of Physicians and Surgeons, New York, NY, USA; [2]Clinics, Sao Paulo, Brazil

In acromegaly, longstanding GH and IGF-1 excess induces marked skeletal changes and increases bone remodeling [1-3]. By DXA, bone mineral density (BMD) varies. The GH receptor antagonist pegvisomant reduces bone turnover markers [4, 5], but in one study 18 months of pegvisomant increased BMD [6]. We examined bone turnover (short-term) and BMD (long-term) in pegvisomant-treated acromegaly patients. 12 patients (4 women, 8 men, ages 19-60 years) were studied before and after 59.5 months (mean) (range 19-136 months) of pegvisomant. 2 women and 2 men were hypogonadal. All had total body (TB) BMD with DXA; 6 patients also had BMD at lumbar spine (LS), hip (TH), and radius. PTH, 25-OH vitamin D, and bone markers were measured in 6 patients at baseline and 36-48 weeks after IGF-1 normalized. Paired t-test compared pre to post treatment values.After pegvisomant, TB, LS, 1/3 and ultra-distal radius BMD increased by 2%, 5%, 1%, and 7%, respectively, and TH BMD decreased by 1% (all p=ns). One male (52.6 yr, hypogonadal) had osteoporosis at the spine (T-score -3.0, -2.7) and ultra-distal radius (T-score -2.9,-2.6) at baseline and after pegvisomant. Bone formation markers decreased: BSAP (32.87 +/- 2.73 vs 22.05 +/- 1.60 U/L (mean ± SE), p=0.002), osteocalcin (18.02 +/- 2.18 vs 12.27 +/- 2.00 ng/mL, p=0.047) and PINP (69.50 +/- 15.69 vs 29.25 +/- 8.49 ug/mL, p=0.0044). NTX (bone resorption marker) did not change (16.62 +/- 3.33 vs 14.6 +/- 4.60 nMol BCE, NS). Calcium and PTH were normal in all patients before and after treatment. Vitamin D was <20 ng/ml in 2 patients.

In this prospective, observational study, BMD was unchanged after long-term pegvisomant treatment that lowered bone formation markers, but not a resorption marker. More studies are needed to better understand the complex interactions between GH, IGF-1, and bone architecture and metabolism.

The authors have no relationship to disclose.

P26

Evaluation of Bone Resistance Parameters in Active and Controlled Acromegaly and Matched Controls with Quantitative CT (QCT)

Elena Valassi[1], Iris Crespo[2], Jorge Malouf[3], Jaume Llauger[4], Ana Maria Marin[3], Betina Biagetti[5], Anna Aulinas[6], Susan M. Webb[7]

Endocrinology/Medicine Departments, Hospital Sant Pau, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unidad 747), ISCIII and Universitat Autònoma de Barcelona (UAB), Endocrinology/Medicine Departments, Spain, Barcelona, Spain[1], Endocrinology/Medicine Departments, IIB-Sant Pau, Hospital Sant Pau, Universitat Autònoma de Barcelona (UAB), ISCIII; Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unit 747), ISCIII. Spain, Barcelona, Spain[2], Medicine, IIB-Sant Pau, Hospital Sant Pau[3], Radiology, IIB-Sant Pau, Hospital Sant Pau[4], Endocrinology, Vall d'Hebron Hospital, Universitat Autònoma de Barcelona. Spain[5], Endocrinology/Medicine, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unidad 747), ISCIII,IIB- Hospital Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain[6], Endocrinology/Medicine Departments, Hospital Sant Pau, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unidad 747), ISCIII and Universitat Autònoma de Barcelona (UAB), Barcelona, Spain[7]

Introduction: GH affects bone metabolism and may affect bone resistance and fractures in active and cured acromegaly. Quantitative CT (QCT) measures bone parameters related to bone resistance. **Aim:** To investigate bone resistance in active and controlled acromegaly and matched controls, using QCT. **Patients & Methods:** 31 acromegaly patients, 18 active -GH>1mcg/L and elevated IGF-I- (46.9±7.8 years, 9 males), 13 controlled (50±7 years, 6 males) and 32 matched controls underwent QCT bone scanning using Mindways Software (Texas, USA) including volumetric BMD (vBMD) and BIT (Bone investigational Toolkit®), after ethical approval. Hip vBMD, cross sectional area (CSA related to bone resistance to compression), average cortical thickness (aCT), and Buckling ratio (BR) of femoral neck (FN) total, trabecular and cortical bone were measured and analyzed by ANOVA. **Results:** Total hip cortical and trabecular vBMD were lower in active acromegaly than controls (816±64.7 vs. 874.9±61 mg/cm3; 118.93±17.3 vs. 142.8±22.8 mg/cm3 respectively, p<0.01); controlled acromegaly had lower total hip trabecular vBMD than controls (124.8±24.8 vs. 142.8±22.8 mg/cm3, p<0.05), but no differences in cortical vBMD. FN total CSA was greater in active acromegaly than controls (12.8±9.3 vs. 8.8±2.1 cm2, p<0.05), and remained in between for controlled patients (9.7+2.1, NS). In active disease, FN aCT (0.4±0.1 vs. 0.33±0.08 cm2, p<0.01) and cortical CSA (5.2±4.1 vs. 3±0.7 cm2, p<0.01) were greater than in controls. No differences were found in BR. In controlled acromegaly, FN aCT was thinner than in active disease (0.3±0.1 vs. 0.4±0.1 cm2, p<0.05), with a similar NS trend for cortical CSA (3.3±0.9 vs. 5.2±4.1 cm2, p=0.079). No differences were observed for FN trabecular CSA between groups. **Conclusions:** vBMD falls in active acromegaly but bone resistance increases compared to controls, due to growth of cortical volume and thickness. After control, cortical parameters (vBMD, CSA, and aCT) did not differ from controls, but trabecular vBMD was still reduced suggesting a higher fracture risk than in active disease.

The authors have no relationships to disclose.

P27

Expression and Correlation of Gsp Oncogene, PKCδ and ERK1/2 in Human Somatotrophinomas

Chen Xi[1], Chen Juan[1], Xie Ruifan[1], Xu Yu[1], Hu Hang[1], Li Ran[1], Ye Fei[1], Liu Qin[2], Lei Ting[1]

[1]Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China; [2]Department of Paediatrics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Objective: To investigate the expression and Correlation of gsp Oncogene, PKCδ and ERK1/2 in Human Somatotrophinomas. **Methods:** Tumor tissues of 54 patients with somatotrophinomas were collected and paraffin embedded. The expressions of PKCδ and ERK1/2 were detected by immunohistochemistry. DNAs of each sample were used for polymerase chain reaction (PCR), and then used for gsp oncogene sequencing. **Results:** Among the 54 cases, gsp oncogene occurred in 11 cases, negative accounted for 43 cases. The expression rate of PKCδ and ERK1/2 were 50% and 51.85%. In gsp oncogene positive cases, the expression rate of PKCδ and ERK1/2 were 45.45% and 36.36%, respectively. In gsp oncogene negative cases, the expression rate of PKCδ and ERK1/2 were 51.16% and 55.81%. In PKCδ positive cases, the expression rate of ERK1/2 was 74.07%, while in PKCδ negative cases, the expression rate of ERK1/2 was 29.63%. **Conclusion:** The expression of PKCδ was associated with ERK1/2, while the expressions of PKCδ and ERK1/2 showed no significant correlation with gsp oncogene.

The authors have no relationships to disclose.

P28

Gigantism: Detailed Clinical Characteristization of a Single Center Series

Vibha Singhal[1,2], Shafaq Khairi[2], Babak Torabi Sagvand[2], Anne Klibanski[2], Madhusmita Misra[1,2], Lisa Nachtigall[2]

[1]Pediatric Endocrinology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [2]Neuroendocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Pituitary gigantism is a rare condition of excess growth hormone (GH) secretion that occurs before epiphyseal fusion leading to tall stature. It is usually isolated but can be associated with MEN-1, McCune Albright syndrome and the Carney complex. AIP mutations and Xq26.3 genomic microduplication have been associated with a subset of cases. Much of the available clinical information stems from case reports and extrapolation of the adult literature in acromegaly. The goal of this study was to describe the clinical characteristics, diagnosis and outcomes in gigantism.

Eleven patients (6 females, 5 males) with gigantism were identified based on elevated IGF-1 or GH, evidence of a pituitary lesion on MRI, or stature more than 2SD above the mean for age. Ten had pathologically confirmed GH staining adenomas (8 macroadenomas; 6 co-stained for prolactin). Most patients presented with tall stature/ skeletal changes (5/11) or visual changes (4/11). The median age of diagnosis was 16 years (IQR: 14-18) with an average delay of 7 (range: 4-13) years since the onset of symptoms. Amenorrhea (primary or secondary), galactorrhea, and hyperprolactinemia were present at diagnosis in 6/6, 0/11, and 2/11 patients respectively. Glucose intolerance, diabetes mellitus (DM), sleep apnea (SA) and hypertension (HTN) were found in 2/11, 1/11, 1/11, and 0/11 respectively. One patient with the longest diagnostic delay (13y) developed left ventricular hypertrophy. The single patient (11%) who achieved surgical remission had a microadenoma. Of eight (73%) who received somatostatin analogs after non-curative surgery, half responded. Five of 9 required post-operative radiation therapy.

Gigantism presents as increased stature or visual loss predominantly with macroadenomas and with a diagnostic delay of many years similar to reports in adult patients. At diagnosis, complications (DM, SA, HTN) are uncommon. Surgical cure rate in patients with gigantism appears to be lower than typically reported in adult patients with acromegaly.

Anne Klibanski receives grant support from Ipsen, Novartis and Rhythm Pharmaceuticals. The other authors have no relationships to disclose.

P29

Glucose and Lipid Levels After Lanreotide Autogel/Depot (LAN) 120mg in Treatment-naïve Patients with Acromegaly: Data from the PRIMARYS Study

Stephan Petersenn[1], John S. Bevan[2], Pascal Maisonobe[3], Caroline Sert[3], Philippe Caron[4] on behalf of the PRIMARYS Study Group

[1]ENDOC Center for Endocrine Tumors, Hamburg, Germany; [2]JJR Macleod Centre for Diabetes, Endocrinology & Metabolism (Mac-DEM), Aberdeen Royal Infirmary, Aberdeen, UK; [3]Ipsen, Boulogne-Billancourt, France; [4]Dept of Endocrinology and Metabolic Diseases, CHU Larrey, Toulouse, France

Introduction: Glucose and lipid abnormalities are common in acromegaly, and somatostatin analogs vary in impact on glucose metabolism. Here, we present glycemic and lipid data for LAN 120mg from PRIMARYS. **Methods:** Treatment-naïve patients with GH-secreting macroadenomas received primary LAN 120mg/4 weeks for 48 weeks (NCT00690898). A priori analyses: A1C, FPG, and lipids; post-hoc analyses: FPG and lipids for patients with hormonal control (HC; GH ≤2.5µg/L with normal IGF-1) and without HC at last post-baseline visit available [LVA]); correlations between IGF-1 changes vs. glycemic and lipid changes. **Results:** 90 patients were treated (mean age, 49.5 years, GH 15.0µg/L, IGF-1 810µg/L); 21.1% with history of diabetes mellitus and 17.8% using previous/concomitant antidiabetes medications. Mean A1C (%) and FPG levels (mmol/L) were stable during the study (A1C: baseline, 6.3; 6.1–6.2 thereafter; FPG: baseline, 6.5; 6.2–6.5 thereafter). There was no deterioration for patients with a history of diabetes (A1C: baseline, 8.0; 6.8–7.4 thereafter; FPG: baseline, 9.1; 7.3–8.8 thereafter) or those without diabetes (A1C: baseline, 5.9; 5.9 thereafter; FPG: baseline, 5.8; 5.9 thereafter). Deterioration of glycemic control to diabetic levels occurred infrequently (A1C ≥6.5% for 1/63, 2/56, 0/47 patients with data at 3, 6, and 12 months, respectively; FPG ≥7.0mmol/L [126mg/dL], for 9/63, 3/62, 5/56). Mean baseline triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol levels were 1.39, 5.05, 3.13, and 1.30mmol/L, respectively. Mean (SD) lipid levels improved slightly after 12 months (–0.20, –0.02, –0.12, +0.20mmol/L). HC was achieved by 30/88 patients at LVA. There was no clear association between HC and glucose and lipid levels (at baseline or changes from baseline to 12 months). There were no correlations between IGF-1 changes vs. glycemic/lipid changes. **Conclusions:** In treatment-naïve acromegalic patients with macroadenomas, 1 year of LAN 120mg had no overall adverse impact on glucose homeostasis and a modest positive impact on lipids.

Sources of research support: Ipsen

Pascal Maisonobe and Caroline Sert are employed by Ipsen; John Bevan is a consultant and speaker for Ipsen; Philippe Caron is a consultant for Ipsen; and Stephan Petersenn is a speaker and member of advisory boards for Ipsen and Novartis.

P30

Incidence of Acromegaly in a Large US Managed Care Population

Tanya Burton[1], Elisabeth Le Nestour[2], Maureen Neary[3], William Ludlam[3]

[1]Optum, [2]inVentiv Health Clinical, [3]Novartis Pharmaceuticals Corporation

OBJECTIVE: To estimate the annual incidence of acromegaly in a large US managed care population, overall and stratified by age, sex, and geographic region, using data from 2008-2012. **METHODS:** Commercial health plan enrollees identified with acromegaly had 2+ medical claims with an acromegaly diagnosis code or one medical claim with an acromegaly diagnosis code in combination with another claim for a pituitary tumor, hypophysectomy, or cranial stereotactic radiosurgery. The first date for an acromegaly-related claim set the index year. Incidence rates were calculated by dividing the number of new acromegaly cases by the calculated person-time at risk. Rates were stratified by age (0-17, 18-44, 45-64, 65+ years), sex (male, female), and US geographic region (Northeast, Midwest, South, West). **RESULTS:** Overall annual incidence rates of acromegaly were relatively constant across 2008-2012 with ~11 cases per million person-years (PMPY). Rates increased with age, ranging from 3-8 cases PMPY among children aged 0-17 to 9-18 cases PMPY among adults aged 65+. Females had 12 cases PMPY on average compared to 10 cases PMPY among men. On average, the Midwest had the lowest incidence rates (7 cases PMPY) compared to the Northeast, South and West (14, 12, and 10 cases PMPY, respectively). **CONCLUSION:** This is the first known study to assess incidence of acromegaly in the US. Results suggest a higher average US incidence rate than previously published studies in Europe, 11 versus 3.3 PMPY (Holdaway, 1999). Using a claims-based approach, this analysis only captured acromegaly patients with an acromegaly-related medical claim. Despite this higher reported incidence, the estimates may actually be an underestimate of the true incidence, as they do not include patients undiagnosed, in remission, or uninsured. While less likely, miscoding may have increased the incidence reported. Additional research is needed to identify the true incidence of acromegaly in the US.

Maureen Neary and William Ludlam are employees of Novartis Pharmaceuticals. The other authors have no relationships to disclose.

P31

Limitations of Current Approaches for Treatment of Acromegaly

Michael H. Shanik[1], William H. Ludlam[2]

[1]Endocrine Associates of Long Island, Smithtown, NY, USA; [2]Novartis Pharmaceuticals, East Hanover, NJ, USA

Background: Acromegaly is a rare disease characterized by hypersecretion of growth hormone (GH), typically from a benign pituitary somatotroph adenoma that leads to subsequent hypersecretion/elevated levels of insulin-like growth factor 1 (IGF-1). Patients with uncontrolled acromegaly have an increased risk of mortality and progressive worsening of comorbidities. Current treatment options include surgery, medical therapy, and radiotherapy, with the overall therapeutic goals of lowering GH levels and achieving normal levels of IGF-1, reducing tumor size, improving comorbidities, and minimizing mortality risk. **Methods:** We evaluated published reports and here we present a summary of the safety and efficacy of current treatment modalities for patients with acromegaly. **Results:** For all currently approved treatment modalities, a significant proportion of patients continue to have persistent elevation of GH and/or IGF-1 levels. Because of the serious health consequences of continued elevation of GH and IGF-1 levels, there is a need for improved therapeutic approaches to optimize the degree and/or duration of biochemical control, particularly in high-need patient populations for whom current treatment options provide limited benefit. Several novel agents are in development, which have the potential to improve the management of patients with uncontrolled or persistent acromegaly. **Conclusions:** Surgery, radiotherapy, and medical therapy each have a proven role in improving clinical outcomes and survival for a substantial proportion of patients with acromegaly who achieve biochemical remission. However, a substantial proportion of patients will not adequately respond to current treatment options, giving rise to a patient population with a high need for improved management options. Without adequate treatment, these patients remain at risk for irreversible health effects associated with uncontrolled acromegaly. There are multiple novel targeted agents currently being evaluated that have the potential to improve management of patients with acromegaly.

William Ludlam is an employee of Novartis Pharmaceuticals; Michael Shanik receives research funding from Novartis Pharmaceuticals.

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

P32

MiR-338-3p as a Tumor Suppressor through Pttg Modulation in GH3 Cell Lines

YangJong Lee[1], Cheol Ryong Ku[2], Eun Jig Lee[2]

[1]Brain Korea 21 PLUS Project for Medical Science, Yonsei University, Seoul, Korea; [2]Endocrinology, Yonsei University College of Medicine, Seoul, Korea

Recent studies suggest that aberrant microRNA expression is common in numerous malignancies. Although miR-338-3phas been implicated in several gastrointestinal cancers, its role in pituitary adenoma is unknown. In this study, we evaluated the role of miR-338-3p on GH secreting pituitary adenoma. Prolactin and growth hormone level in rat pituitary GH-producing (GH3) cells were markedly down-regulated after inhibition of miR-338-3p, however, miR-338-3p and prolactin level was highly up-regulated after estrogen (E2) treatment. These results demonstrate that miR-338-3p affects hormonal system of GH3 cells and compensate for the tumorigenic condition. Same pattern of these results is also shown in human pituitary adenoma tissue. miR-338 targeted pituitary tumor transforming gene (Pttg), which is an important paracrine growth factor involved in early lactotrope transformation and early onset of angiogenesis in pituitary hyperplasia. Our findings provide the evidence of tumor suppressor function of miR-338-3p in pituitary adenoma in acromegalic patients and highlight the concurrent effect of compensation in the pathogenesis of pituitary adenoma.

The authors have no relationships to disclose.

P33
Need for Improved Monitoring in Patients with Acromegaly

Julie M. Silverstein

Division of Endocrinology, Metabolism and Lipid Research, Washington University School of Medicine, St. Louis, MO, USA

Background: Acromegaly is a rare disease characterized by overproduction of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) and is associated with increased mortality risk and progressive worsening of disease-related comorbidities. Multimodal treatment with surgery, medical therapy, and radiotherapy provides biochemical control (normalization of IGF-1 and reduction of GH to <2.5 ng/mL) to a substantial proportion of patients. Because patients with acromegaly must undergo long-term treatment, monitoring of IGF-1 and GH levels plays a key role in management, especially for the detection of persistent or recurrent disease. While there is a good consensus regarding the treatment algorithm for patients with acromegaly, guidance is less defined regarding what constitutes optimal monitoring for these patients. **Methods:** An examination of current ENDO and AACE guidelines was performed to identify specific recommendations regarding monitoring of patients with acromegaly. **Results:** Current AACE guidelines identified that oral glucose tolerance tests and assessments of IGF-1 levels should be performed annually for all patients, and frequent and long-term monitoring of IGF-1/GH levels should be conducted in patients who achieve biochemical remission following treatment. Guidance on patients with discordant IGF-1 and GH levels and on optimal timing of evaluations and duration of testing is less definitive. The published ENDO guidelines include recommendations on monitoring for patients treated with somatostatin analogs (SSAs). Specifically, measurement of serum IGF-1 and GH should be performed after 12 weeks, just prior to administration of the next dose of drug, and glucose-suppressed GH values during treatment with SSAs have limited utility. **Conclusions:** Given that monitoring is so intimately linked to the successful management of patients with acromegaly, we propose potential areas of improvement for the current monitoring algorithm of patients with acromegaly, including the potential for more frequent monitoring and/or incorporation of additional disease markers to monitor patients.

The author has no relationships to disclose.

P34
No Excess Long-Term Mortality in the Finnish National Acromegaly Cohort – A Twenty-Year Follow-up Study

Elina Ritvonen[1], Jari Haukka[2], Emmi Tikkanen[2, 3], Ritva Kauppinen-Mäkelin[4], Camilla Schalin-Jäntti[1]

Division of Endocrinology[1], Department of Medicine, Helsinki University Central Hospital and University of Helsinki, and Hjelt Institute[2], University of Helsinki, and Institute for Molecular Medicine Finland[3], and Department of Internal Medicine[4], Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland

Objective: We recently reported that to date, hormonal control can be achieved in 90% of Finnish FPA patients (n=100)(1) and wanted to study if this might translate into normal mortality rates for the Finnish national acromegaly cohort compared to age- and gender-matched controls after long-term follow-up. **Patients and methods:** We assessed all-cause mortality in a nation-wide cohort of 333 Finnish acromegaly patients diagnosed between years 1980 and 1999. Patients were followed up until the end of 2013. Survival rates were compared to the age- and gender-matched sample from the Finnish general population (n=4995) with log-rank test and Kaplan-Meier curves. Multivariate Cox's regression was used to estimate the hazard ratio (HR) of all-cause mortality. **Results:** Of the 333 patients (52% women) with acromegaly, 113 (34%) died during the mean follow-up period of 20.0 years. There were 1548 deaths (31%) in the control population. Mortality rates (per 1000 person-years) for patients did not differ from those of the background population, 5.0 (95%CI 4.12-6.02) vs 4.6 (95%CI 4.41-4.89), P=0.436. Surgery as primary treatment was performed in 86.5% of cases and 43.5% received radiotherapy. In the general population, female gender predicted lower mortality (HR 0.53, 95%CI 0.48-0.59, P<0.001), but in patient population, no association between gender and mortality was detected (HR for women 1.08, 0.74-1.57, P=0.688). Tumor size, or serum growth hormone concentration at the time of diagnosis were not associated with mortality. **Conclusions:** According to this 20-year follow-up study of the Finnish national acromegaly cohort, long-term outcome of patients is good, with no increase in mortality rates compared to the general population. In the patient population, no over-mortality in men was observed compared to the background population.

The authors have no relationships to disclose.

P35

Pituitary Gigantism: Long-term Follow-up of 13 Cases

Beatriz Lecumberri[1], Nuria Palacios[2], José García-Uría[3], Tomás Lucas[4]

[1]Endocrinology and Nutrition Department, La Paz University Hospital, Madrid, Spain; [2]Endocrinology and Nutrition Department, Puerta de Hierro University Hospital Madrid, Spain; [3]Neurosurgery Department, Puerta de Hierro University Hospital, Madrid, Spain; [4]Endocrinology and Nutrition Department, Sanchinarro University Hospital, Madrid, Spain

Pituitary gigantism results from GH hyperproduction before epyphisis closure. From our series of 520 patients with acromegaly we have revised 13 (2.5%) with gigantism, 11 males and 2 females. Mean age at first symptoms was 14.6 + 8.9 years, and mean age at diagnosis was 21.6 + 4.8 years, so a mean delay of 7 seven years was found between both events. Mean final height and weight were 192.6 + 10.2 (range 1.80-2.16 cm) and 110.9 + 11.4 (89-124 kg), respectively. Mean paternal and maternal height were 182.3 + 12.1 and 166.7 + 7.1 cm, respectively. Tall relatives were reported by one patient. At diagnosis all patients referred acral overgrowth (mean shoe size: 45.6 EU), 12 facial and skin changes, 8 sweating, 7 carpal tunnel syndrome, 6 headaches, 5 visual fields defects, 4 joint pain, 2 sleep apnea, and one had hypogonadism and pituitary apoplexy. Mean GH was 31.6 + 22.2 ng/ml, GH after OGTT 28.9 + 21.2 ng/ml, IGF-1 1019.4 + 465.9 ng/ml, PRL 94.5 + 179.8 ng/ml (normal range 2.1-17.7). On presurgical pituitary imaging, mean tumor dimensions were 26.9 x 24.4 mm, 12 patients had extrasellar extension and 9 invasion. All patients were first operated using a transsphenoidal approach, 3 were re-operated and 9 treated with postoperative radiotherapy: 7 conventional radiotherapy, 1 stereotactic radiotherapy and 1 radiosurgery. Two patients were re-irradiated using radiosurgery. At the time of the study (mean follow-up 24 + 7.4 years (34-16)) 6 patients had achieved definitive cure (46.1%), 5 were controlled on pharmacological treatment (38.4%) and 2 were lost for the follow-up. Ten patients (76.9%) had at least one pituitary deficiency: 9 gonadal, 6 thyroid and adrenal, and 1 diabetes insipidus. Mean time from diagnosis to definitive cure was 6.7 + 4.1 years (0.3-13).

The authors have no relationships to disclose.

P36

Potential Factors Related to Treatment Changes in Acromegaly Patients: Analysis of a U.S. Prospective Registry

Carmichael JD[1], Mamelak A[2], Broder MS[3], Neary MP[4], Chang E[3], Cherepanov D[3], Ludlam WH[4], Bonert V[2]

[1]University of Southern California, Los Angeles, CA, USA; [2]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [3]Partnership for Health Analytic Research, LLC, Beverly Hills, CA, USA; [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

OBJECTIVES: Acromegaly is treated with surgery, followed by pharmacotherapy if biochemical values are uncontrolled. We identified factors related to treatment changes in acromegaly. **METHODS:** Patients in the Cedars-Sinai Pituitary Center Acromegaly Registry were classified as biochemically-controlled (IGF-I≤ULN, GH nadir <1.0µg/L ≤2 hours following OGTT, random GH level <1µg/L, or mean integrated 24-hour GH <2.5µg/L), uncontrolled (abnormal), or discordant (1 normal, 1 abnormal). Treatment change was defined as pharmacotherapy after radiation or surgery, change in medication, or additional radiation or surgery. Prevalence of diabetes mellitus (DM) and hypertension (HTN) were compared in controlled vs. uncontrolled patients. **RESULTS:** Over a mean 8.8 years, there were 240 evaluable treatment changes in 73 patients. 61 patients were initially treated with surgery, 11 medically, and 1 with radiation. Among 61 surgical patients progressing to a second therapy, 52 (85%) were biochemically-uncontrolled, 6 (10%) were discordant, and 3 (5%) were controlled. Among 11 medically treated patients progressing to a second therapy, 7 (64%) were uncontrolled, 2 (18%) were discordant, and 2 (18%) were controlled before their next treatment. 73 patients underwent 167 subsequent treatment changes. Patients were uncontrolled prior to changing treatment in 117 (70%) cases, discordant in 16 (10%), and controlled in 34 (20%). Comparing uncontrolled (n=35) versus controlled (n=70) patients at study end, 15 (43%) vs. 18 (26%) had DM and 21 (60%) vs. 30 (43%) had HTN. **CONCLUSIONS:** Most treatment changes were preceded by abnormal lab parameters, suggesting physician recognition of the long-term importance of biochemical control with adjustment of treatment accordingly. However, therapy was switched in controlled patients possibly due to therapy intolerance, persistent or new symptoms, or cost. Biochemically uncontrolled patients had higher rates of DM and HTN than those who were controlled. Varieties of therapeutic options are required since biochemical control is not the only determinant of drug choice.

John Carmichael receives research support and honoraria from Novartis, and honoraria from Pfizer and Genentech; Michael Broder, Eunice Chang, and Dasha Cherepanov are employees of Partnership for Health Analytic Research, LLC, a health services research company paid by Novartis to conduct this research; Maureen Neary and William Ludlam are employees of Novartis Pharmaceuticals; The other authors have no relationships to disclose.

P37
Quality of Life in Patients with Acromegaly

Shingo Fujio[1], Hiroshi Arimura[2], Mika Habu[1], Hirofumi Hirano[1], Manoj Bohara[1], Kazunori Arita[1]

[1]Department of Neurosurgery, Graduate School of Medical and Dental Sciences, Kagoshima University, Japan; [2]Department of Diabetes, Metabolism and Endocrinology, Graduate School of Medical and Dental Sciences, Kagoshima University, Japan

Introduction: Patients with acromegaly reportedly have compromised quality of life (QOL) which may persist despite long-term remission. But, exact effect of surgical control of acromegaly on postoperative physical and psychological aspects of QOL is not fully understood. The aim of the present study was to assess pre- and postoperative QOL in acromegalic patients. **Materials and Methods:** We assessed QOL in 30 acromegalic patients cured solely by surgery using the SF-36 questionnaire. The judgment of cure was based on Cortina consensus criteria; nadir GH < 1μg/L during postoperative oral glucose tolerance test (OGTT) and normal IGF-1 level. The Statflex software program (version 6.0) was used for statistical analysis of the results. This retrospective study was approved by the Kagoshima University Hospital Ethical Committee (Reference no 402). **Results:** Before operation, almost all parameters of SF-36 in acromegalics were below the set standards of normal population. There were no correlations between physical component summary (PCS) or mental component summary (MCS) scores and patient's age, sex, tumor size, preoperative GH level, SD score of IGF-1 level, or number of comorbidity. After operation, the PCS score did not change, but the MCS score significantly improved. There were no statistical differences in PCS or MCS scores between 19 patients with nadir GH < 0.4μg/L during postoperative OGTT and 11 patients with nadir GH 0.4-1.0 μg/L. **Conclusion:** Remission provided by surgery improved psychological subscale of QOL in the short term. The long term effect of surgery and the effect of employing the new and stringent criteria of cure should be checked by prolonged follow-up with further accumulation of subjects.

The authors have no relationships to disclose.

P38
Radiation-induced Sarcoma in Patients with Acromegaly

Tomris Erbas[1], Ayse I. Colpak[1], Kamil Oge[1], Feyza Onder[2], Kader Karlı Oguz[1], Figen Soylemezoglu[1], Ilkay Isikay[1], Selcuk Palaoglu[1], Selcuk Dagdelen[1], Tulay Kansu[1], Faruk Zorlu[1]

[1]Hacettepe University Medical School-Ankara, Turkey; [2]Haseki Training and Research Hospital-Istanbul, Turkey

Radiotherapy has several long-term complications, of which development of radiation-induced neoplasm being relatively rare. To date, only 50 cases were reported of devoloping sellar sarcomas after radiotherapy for pituitary adenomas. Here, we present two patients with acromegaly who developed sarcoma in the sellar region after radiotherapy. Case 1: A 36-year-old female was admitted with a history of headache and enlargement of her extremities. Laboratory tests confirmed acromegaly. MRI exhibited a macroadenoma with suprasellar and left cavernous sinus extension. She underwent a subtotal resection, and radiotherapy of 56 Gy was administered. In addition, SSA was given for the next five years. The patient presented seven years later with diplopia and headaches. MRI demonstrated the presence of a giant lesion within the pituitary region, with invasion into the bilaterally cavernous and sphenoidal sinuses and nasopharynx. The tumor was subtotally removed and a histological diagnosis of sarcoma was made. Despite treatment with chemotherapy, the tumor progressed, and she died two months later. Case 2: A 56-year-old female was diagnosed with acromegaly at the age of 40 years. She had undergone a resection of the pituitary macroadenoma. Surgery was followed by radiotherapy (54 Gy) and she required treatment with SSA. She also had a diagnosis of thyroid papillary carcinoma. Fifteen years after radiotherapy, she presented with deterioration of her visual acuity in the left eye. MRI showed subtle thickening and contrast enhancement of the optic nerves suggesting radiation-induced optic neuropathy. Despite the corticosteroid, hyperbaric oxygen and bevacizumab therapy, she developed visual impairment also in the right eye. One year later, the patient was readmitted to the hospital because of severe headache. MRI showed an enhancing mass suggestive of high grade optic glioma in both optic nerve. The patient underwent debulking surgery and a histological diagnosis of sarcoma was made.

Clinicians should consider secondary neoplasm risk in acromegalic patients undergoing radiation therapy.

The authors have no relationships to disclose.

P39

The Value of Acute Octreotide Suppression Test in Predicting Short-term Efficacy of Somatostatin Analogues in Acromegalic Patients

Ming Shen[1], Meng Wang[2], Yongfei Wang[1], Hongying Ye[2], Yiming Li[2], Shiqi Li[1], Yao Zhao[1], Zhaoyun Zhang[2]

[1]Department of Neurosurgery, [2]Department of Endocrinology, Huashan Hospital, Fudan University, Shanghai, China

Introduction: The usefulness of the acute octreotide suppression test (OST) in predicting the response to somatostatin analogues (SSAs) treatment in acromegalic patients is controversial. The aim of the study was to determine the value of OST in predicting the short-term efficacy of SSAs. **Methods:** We conducted a prospective study at a single tertiary healthcare centre. Sixty-seven newly diagnosed and treatment-naive acromegalic patients underwent 100μg subcutaneous OST. Then all patients were treated with SSAs (44/67 octreotide LAR; 23/67 lanreotide SR) for 3 months. Biochemical response was defined as a post-treatment mean growth hormone (GH_m) in GH day curve < 2.5 μg/l or >75% fall compared with the pre-treatment mean GH. Tumor response was defined as the tumor volume shrinkage >20%. **Results:** We used 9 parameters derived from the OST to predict short-term efficacy of SSAs, which included GH_n (the nadir GH during the OST), △GH1(=[GH_{0h}-GH_n]/GH_{0h}), △GH2(=[GH_m-GH_n]/GH_m), $AUC_{(0\text{-}6h)}$ (the GH area under curve during the OST), △AUC1 (=[GH_{0h}- $AUC_{(0\text{-}6h)}$]/ GH_{0h}), △AUC2 (=[GH_m- $AUC_{(0\text{-}6h)}$]/GH_m), $AUC_{(m\text{-}6h)}$ (the GH AUC during the OST when GH_m was used instead of GH_{0h}), △AUC1'(=[GH_{0h}-$AUC_{(m\text{-}6h)}$]/GH_{0h}) and △AUC2'(=[GH_m-$AUC_{(m\text{-}6h)}$]/GH_m). Compared with other parameters, △GH2, △AUC2 and △AUC2' showed both better positive predictive value (PPV) and better negative predictive value (NPV) (85.7% and 93.8%, respectively) in predicting biochemical response. In addition, △GH2 was better than other 8 parameters in predicting tumor response (PPV 87.5% and NPV 84.8%). **Conclusions:** △GH2 derived from OST and GH_m is a useful index in predicting both biochemical response and tumor shrinkage of short-term SSAs treatment in acromegalic patients.

The authors have no relationships to disclose.

P40

Treatment of More than 5-week Interval of Octreotide LAR in Patients with Acromegaly

Izumi Fukuda, Naomi Hizuka and Atsuhiro Ichihara

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

Background: The efficacy of octreotide LAR for patients with acromegaly has been demonstrated. Usually, octreotide LAR is administered intramuscularly every 4 weeks. However, there is a subset of patients who are very sensitive to octreotide. In such cases, dose down titration or an extended injection interval could be considered. **Objective:** In this study, we retrospectively evaluated changes in GH and IGF-I levels during extended interval of octreotide LAR injection in patients with acromegaly who have had well-controlled with 4-week injections. **Patients and Methods:** The intervals of long-acting somatostatin analogue (SA) were extended to more than 5 weeks in 4 patients with acromegaly (M/F 1/3, age: 31-64 years old) who were stable during 10 mg of one-monthly injection of octreotide LAR. Serum GH and IGF-I levels of just before the following administration were evaluated during prolonged injection intervals. **Results:** Serum IGF-I levels remained normal during 6-week interval in all but 1 patient. The levels remained normal during 9 to 11 week intervals in two of these patients. All patients underwent trans-sphenoidal surgery, and two patients received gamma-knife prior to octreotide LAR therapy. Basal GH levels before octreotide LAR therapy ranged from 2.47 to 11.7 ng/ml and IGF-I SDS ranged between 2.0 ~ 7.5 SD. The median treatment period of long-acting SA was 96 months (range: 36 to 113 months) and initial doses of octreotide LAR were 10 mg/M in 3, and 20 mg/M in one patient. **Conclusion:** Extended interval of octreotide LAR injection might be able to consider in patients who are well-controlled during 10 mg/4-week injections, though the dosing interval should be adjusted individually. This attempt might be not only good for cost saving but also reducing the burden of patients.

The authors have no relationships to disclose.

P41

Treatment Patterns Among United States Acromegaly Patients in a Prospective Registry

Carmichael JD[1], Mamelak A[2], Broder MS[3], Neary MP[4], Chang E[3], Cherepanov D[3], Ludlam WH[4] Bonert V[2]

[1]University of Southern California, Los Angeles, CA, USA; [2]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [3]Partnership for Health Analytic Research, LLC, Beverly Hills, CA, USA; [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

OBJECTIVES: Surgery is classically first-line therapy for acromegaly, followed by pharmacotherapy. Data on real-world acromegaly treatment patterns in the United States are limited. **METHODS:** Sequential therapeutic interventions, duration of pharmacotherapy, and time to next treatment were analyzed from the Cedars-Sinai Pituitary Center Acromegaly registry. Short courses of pre-surgical pharmacotherapy and test doses of octreotide-SA before longer-acting somatostatin receptor ligands (SRLs) were excluded from analysis. Patient data, including therapy prior to enrollment, were entered into the registry at the time of the first Pituitary Center visit. **RESULTS:** 121 patients (mean age 55.4 years, 55.4% female) were followed for mean 8.8 years. First-line therapy was surgery in 104 patients (86%), pharmacotherapy in 16 (13%), and radiation in 1 (1%). Of the 104 patients with initial surgery, 78 (75%) underwent further therapy: 7 (9%) underwent second surgery, 67 (86%) received pharmacotherapy (72% SRLs, 28% dopamine agonists), and 4 (5%) radiation. Median time from first-line surgery to second-line therapy was 369 days. In 104 patients treated with initial surgery, 38 (37%) received second-line therapy within the first year, with 28 (27%) receiving second-line therapy within the first 6 months. An additional 40 (38%) patients required second-line therapy after mean of 3.0 years. Of 16 patients on first-line pharmacotherapy, 13 (81%) subsequently received further treatment (5/13 [38%] within 1 year); 4/13 had surgery and 9 /13 had further pharmacotherapy. **CONCLUSIONS:** Data from a prospective tertiary referral center disease registry demonstrates persistent acromegaly in 37% of patients within the first year after first-line surgical intervention. Second-line therapy largely comprised medical treatment, predominately with SRLs. While short-term postoperative remission rates are high, several patients required second-line therapy years after initial surgery, further supporting the need for long-term biochemical surveillance in acromegaly to detect disease recurrence.

Maureen Neary and William Ludlam are employees of Novartis; Michael Broder, Eunice Chang, and Dasha Cherepanov are employees of Partnership for Health Analytic Research, LLC, a health services research company paid by Novartis to conduct this research; John Carmichael receives research support and honoraria from Novartis, and honoraria from Pfizer and Genentech. The other authors have no relationships to disclose.

MISCELLANEOUS

P42

A Retrospective Study on 51 Cases of Hypothalamic Syndrome and Metabolic Complications in Peking Union Medical College Hospital

Huijuan Zhu*[1], Xiaoxing Gao[1], Hui Pan[1], Yong Yao[2], Renzhi Wang[2], Feng Feng[3]

[1]Department of Endocrinology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Key Laboratory of Endocrinology of Ministry of Health, BEIJING, China; [2]Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, BEIJING, China; [3]Department of Radiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, BEIJING, China

Aim: Hypothalamic syndrome (HTS) is a rare syndrome with known causes of hypothalamus lesions (neoplastic, vascular, malformation) or idiopathic. Our goal is to summarize the clinical features and complications of patients with hypothalamic syndrome in Peking Union Medical College Hospital (PUMCH) and improve the diagnosis and intervention strategy of HTS. **Method:** 51 patients were included in the study who were diagnosed with HTS in PUMCH from 1989 to 2014. The etiologies, clinical manifestations, metabolic parameters including lipid profiles, glucose level and blood pressure of these patients were analyzed. **Results:** Gender ratio (male/female) is 1:1.13. 47.1% patients were under 18-year-old. Surgical operations and neoplasm were the most common causes of HTS. Patients with natural courses accounted for 66.7% while in other cases, symptoms were caused or exacerbated by evasive interventions such as surgeries. Hyperthermia, hyperphagia and hypodipsia were common symptoms at onset. Cases with an acute onset were related to surgical operations. Non acute hypothalamic syndrome were prone to overweight/obesity, hyperlipidemia and impaired glucose tolerance/diabetes with diagnose rates of 52.9%, 56.9%, 35.3% respectively. **Conclusion:** We here propose for the first time to categorize HTS patients according to the onset of disease, which is an effective way to predict the manifestations and outcomes in our study. Usually the onset of non-acute hypothalamic syndrome is slow thus close monitoring is necessary. In addition to hormone replacement therapy for affected endocrine glands, long-term management of metabolic complications are of vital importance.

The authors have no relationships to disclose.

P43

Diagnostic Challenges in Pituitary Stalk Lesions: A Single Center Experience Over 10 Years

A Ram Hong, Ji Hyun Lee, Dong-Hwa Lee, Ji Won Yoon, Jung Hee Kim, Sang Wan Kim, Chan Soo Shin and Seong Yeon Kim

Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea

The etiologies of disease presenting with pituitary stalk lesion are various. Due to the critical location of pituitary stalk in surgical biopsy and risk of hypopituitarism after procedure, the diagnosis often depends on clinical presentation and imaging findings. The aim of the present study was to review the diagnostic work-up the causes and natural courses of pituitary stalk lesions for 10 years.

We retrospectively reviewed the medical records of 71 patients with pituitary stalk lesions aged over 16 years seen at Seoul National University Hospital from 2004 to 2014.

Thirty-two of 71 patients (45%) had underlying malignancy. All germ cell tumors (n=10) occurred in patients <35 years old, and were confirmed with biopsy of stalk lesions (n=7) or cerebrospinal fluid cytology (n=3). Langerhans cell histiocytosis (n=6) was diagnosed with biopsy of skull, lung and liver (n=4) and biopsy of stalk lesions (n=2). IgG4-related pituitary disease was diagnosed in one patient with underlying disease and newly diagnosed in one patient with transsphenoidal surgery. Twenty (28%) patients with isolated stalk lesions and no visual symptoms have not been pathologically proven and followed without treatment. Diabetes insipidus (DI) was initially found in 11 patients (55%), and gonadotropin axis and growth hormone deficiency was presented in 5 (25%) and 3 (15%) patients, respectively. During the follow-up, thickened stalk lesions decreased in 9 (45%), did not change in 10 (50%), and increased in only one patient (5%). DI was improved in 3 (15%) patient. Gonadotropin dysfunction newly developed in 3 (15%), and improved in 2 (10%) patients

Evaluation for pituitary stalk lesions needed the work-up for malignancy and inflammatory diseases. In patients with isolated pituitary stalk lesions without visual symptom can be followed-up without biopsy monitoring hormone function and mass effect. However, early biopsy should be considered in patients under 35 years old.

The authors have no relationships to disclose.

P44

Endoscopic Biopsies of Lesions Associated with a Thickened Pituitary Stalk

Yong Yao[1], Kan Deng[1], Hui-juan Zhu[2], Lin Lu[2], Ming Feng[1], Xin-jie Bao[1], Ren-zhi Wang[1]

Department of Neurosurgery[1], Department of Endocrinology[2] Peking Union Medical College Hospital, Beijing,China

Background: Lesions associated with a thickened pituitary stalk have a diverse pathology. For clinical decision- making, it is necessary to make a diagnosis based on pathological biopsy of the lesions. The objectives of this study were to discuss the indications for and timing of a diagnostic neurosurgical procedure in patients with a thickened pituitary stalk (TPS) on magnetic resonance (MR) imaging, review endoscopic biopsies of the TPS lesions and to assess the Multidisciplinary Collaboration for management of these lesions. **Methods:** 23 patients (8 males and 15 females) aged from 8 to 38 years, who presented with diabetes insipidus(DI) and anterior pituitary hypofunction underwent endoscopic biopsy of a pituitary stalk lesion between 2010 and 2014 at PUMCH(Peiking Union Medical College Hospital). The relationships of the extent of lesions with surgical approaches were retrospectively examined. **Results:** Among the 23 patients, a biopsy was performed via an endoscopic transsphenoidal approach for 13 with pituitary stalk associated with intrasellar lesions; via an endoscopic extended transsphenoidal approach for 9 with pituitary stalk localized lesions; and via an endoscopic intraventricular approach for 1 with the lesion protruding from the infundibulum. 1 patient occurred cerebrospinal fluid leakage after operation which demand a second surgery. Pathological examinations of all the lesions confirmed diagnoses of germinoma in 21 patients, Langerhans cell histiocytosis in 2 patients. None of the 23 patients had further deterioration of pituitary function postoperatively. **Conclusions:** Patients with a significant TPS (pituitary stalk thickness >5.0mm) or a radiological deterioration are appropriate for surgical biopsies. Endoscopic biopsy of pituitary stalk lesions is a microinvasive way compared to transcranial biopsy. The endoscopic transsphenoidal approach is suitable for biopsies of pituitary stalk lesions associated with intrasellar lesions. Otherwise, the endoscopic intraventricular approach seems suitable for intraventricular lesions, and the endoscopic extended transsphenoidal approach appears appropriate for localized pituitary stalk lesions.

The authors have no relationships to disclose.

P45

MSH3 Gene Missense Mutation as a Novel Molecular Pathogenesis of Dedifferentiated Chondrosarcoma in the Pituitary Region, a Sequencing-based Study

Lu Gao, Xiao-Peng Guo, Bing Xing, Yong Yao, Ren-Zhi Wang

Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

The objective of the study was to illustrate the molecular pathogenesis of dedifferentiated chondrosarcoma (DDCS) in the pituitary region. It was a middle-aged male patient with severe cephalalgia and vision loss of the right eye. The patient underwent transsphenoidal surgery and died three months after surgery. The formalin-fixed, paraffin-embedded specimen of the patient was pathological diagnosed as DDCS. Under pathological inspection, the specimen could be categorized as a well-differentiated component and a dedifferentiated component. Micro-dissections were conducted to yield tissue that contained only the well-differentiated component or the dedifferentiated ones. Both components of the tissue underwent DNA extraction and subsequent target-next generation sequencing. The sequencing panel covered the exon regions of five hundred and eight cancer-associated genes, which included frequently-mutation genes in chondrosarcoma, such IDH1, IDH2, and TP53. Both components yielded with the same missense mutation of MSH3 gene. No mutations were found in the exon regions of IDH1, IDH2, or TP53 genes. Thus, MSH3 gene missense mutation serves as the causing factor in this case of DDCS in the pituitary region, for both well-differentiated and dedifferentiated components. Both components, though morphological distinct from one another, should rise from the cell of the same origin. This study was approved by the Ethical Committee of Peking Union Medical College Hospital. Informed consent was obtained from the patient.

The authors have no relationships to disclose.

P46

Secondary Hypothyroidism and an Enlarging Sellar Mass: An Unusual Case of Primary Pituitary Lymphoma

Desai, Kaniksha; Chindris, Ana; Bernet, Victor; Meek, Shon

Department of Endocrinology, Mayo Clinic, Jacksonville, FL, USA

Background: Primary Pituitary Lymphoma (PPL) is a rare form of primary CNS lymphoma, which accounts for 3% of intracranial neoplasms. PPL can present with symptoms of hypopituitarism and cranial nerve palsies similar to pituitary adenomas and is sometimes difficult to diagnose prior to surgery. **Case:** A 60 year old female with no significant past medical history presented to the ER with nausea and vomiting and was found to have hyponatremia. Laboratory workup included a TSH of 0.01 mIU/L and a FT4 of 0.4 ng/dl. Due to her secondary hypothyroidism, she had an MRI of the brain which revealed a 19 X 11 mm sellar mass. There was no optic chiasm compression or cavernous sinus invasion. The mass was presumed to be a pituitary adenoma. Clinical examination was normal. Labs showed a normal prolactin, serum and urinary cortisol, and IGF1 level. The patient declined surgery and levothyroxine was started. She presented back to the ER 3 months later with a severe headache and vision loss. Clinical examination now showed ptosis of the left eye. This raised concern for an episode of pituitary apoplexy. A repeat MRI revealed an expanding sellar mass, now measuring 24 x 20 mm with optic chiasm bowing and cavernous sinus invasion but no hemorrhage. She had a transphenoidal pituitary resection with residual tumor of 8 mm which doubled in size in 2 weeks. Pathology revealed a high grade B-cell lymphoma. A CT scan of chest, abdomen, and pelvis was completed as well as bone marrow biopsy which did not reveal other sites of lymphoma. Chemotherapy with an RCHOP and methotrexate regimen was started with subsequent regression of her tumor. **Conclusion:** Pituitary lymphomas can be difficult to diagnose on imaging, but should be considered when evaluating sellar masses, especially enlarging masses with new onset hypopituitarism and worsening symptoms.

The authors have no relationships to disclose.

P47

Sellar Paraganglioma: A Case Report with 10 Year Follow-up

Stephanie Cox[1], John V Conaglen[1,2], Marianne S Elston[1,2]

[1]Department of Endocrinology, Waikato Hospital, Hamilton, New Zealand; [2]Waikato Clinical School, University of Auckland, New Zealand

Background: Paragangliomas of the sellar and parasellar region are very rare, with only 16 previously described cases. There is limited evidence to guide management, which has traditionally consisted of surgical resection +/- adjuvant radiotherapy. **Clinical Presentation:** A 66yr old woman presented with a 1 day history of headache and diplopia with a right 3rd cranial nerve palsy. Pituitary function was normal. On MRI a mass lesion was seen arising from the pituitary fossa, invading the right cavernous sinus and wrapping around the right internal carotid artery. The initial diagnosis was a pituitary macroadenoma. **Intervention:** Trans-sphenoidal debulking was undertaken with post-op resolution of the 3rd nerve palsy. Histology confirmed a gangliocytic paraganglioma. The patient did not receive adjuvant radiotherapy and was managed expectantly. At 10 year follow-up MRI appearances are unchanged and the patient remains well. **Conclusion:** We present a rare case of sellar paraganglioma. At 10 years, this case describes the longest follow-up period reported to date. The patient has remained asymptomatic, with intact pituitary function. In sellar/parasellar paragangliomas with benign histological features adjuvant radiotherapy may not be necessary.

The authors have no relationships to disclose.

PITUITARY ADENOMA

P48
Expert Consensus for Surgical Treatment of Pituitary Adenoma in China

Ren-Zhe Wang, Chinese Pituitary Adenoma Cooperative Group

Departments of Neurosurgery, Neurosurgical Center of Pituitary Tumors, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Pituitary adenoma is a benign tumor and surgical treatment is the main method for the treatment of patients with various types of pituitary adenomas. If treated properly, most patients can be cured. However, China is vast in territory with unbalanced economic development and uneven medical level. Understanding and treatment of the disease have very big difference. These factors have seriously affected the prognosis of the patients with pituitary adenoma. **Methods:** In order to solve the above problems, to improve the level of surgical treatment of pituitary adenoma, Chinese Pituitary Adenoma Cooperative Group organized experts and scholars to write "Expert consensus for surgical treatment of pituitary adenoma in China". We hope that this consensus can enhance the understanding of surgical treatment for pituitary adenoma and standardize surgical treatment of pituitary adenoma in China. **Results and Conclusions:** This consensus introduces the principles of diagnosis, treatment, follow-up and other relevant surgical treatment of pituitary adenoma, and especially focuses on the peri-operation period treatment, operation indication, operation approaches and the treatment of various complications. Because of the complexity and diversity of pituitary adenoma itself, the treatment process will encounter various problems. We hope that pituitary consultation centers should be established in the hospitals, including these departments such as Neurosurgery, Endocrinology, Obstetrics and Gynecology, Radiology, radiotherapy and others. The majority of patients with pituitary adenomas should also be advised to visit such "pituitary consultation centers" in the hospitals for diagnosis and treatment, in order to get the best curative effect.

The author has no relationships to disclose.

P49
Extended Transsphenoidal Approach for Pituitary Adenomas Invading the Cavernous Sinus Assisted by Multiple Techniques

Xin-Jie Bao, Ren-Zhi Wang

Department of Neurosurgery, Peking Union Medical College Hospital, Beijing, China

Objective: We describe our surgical experience to remove pituitary adenomas invading the cavernous sinus (CS) and analyze what factors influencing the degree of tumor resection and occurrence of complications. **Methods:** Retrospective analysis was performed in 52 patients with pituitary adenomas extending into the CS that were surgically treated via the extended transsphenoidal approach assisted by multiple techniques including microscope, endoscope, neuronavigation, and intraoperative Doppler ultrasonography. The extent of resection and clinical outcomes were compared between Knosp Grade 3 and Knosp Grade 4, additionally between first operation and reoperation. This study was approved by the Ethical Committee of Peking Union Medical College Hospital. **Results:** Gross-total resection (GTR) was achieved in 33 patients (63.5%). The rate of GTR was significantly different stratified by Knosp Grade category (Knosp Grade 3: 92.3% vs. Knosp Grade 4: 53.8%, p = 0.01). GTR of tumor in patients with first operation was significantly higher than in patients with reoperation (77.1% vs. 35.3%, p = 0.003). Only 1 transient cranial nerve palsy (2.9%) was occurred in first operation without other postoperative complications, however, it was significantly higher in reoperation. In addition, firm tumor consistency was very common in patients who had received previous surgery (reoperation: 52.9% vs. first operation: 8.6%, p = 0.0004). **Conclusions:** The extended transsphenoidal surgery assisted by multiple techniques for pituitary adenomas invading the CS has proven to be highly effective, especially for tumors belonging to Knosp Grade 3 or first operation. It should be noted that total removal of pituitary tumors highly invading the CS, which are firm and regional anatomy is distorted by scar tissues because of previous surgery, remains a big challenge.

The authors have no relationships to disclose.

P50

Non Suspected Thyrotropinoma: 15 Years Follow-up

Lopez, Florencia; Guitelman, Mirtha Adriana

Endocrinology Division, Hospital Carlos G Durand, Buenos Aires, Argentina

Introduction: TSH-secreting pituitary adenomas (TSHoma) are the less frequent adenomas (0.5- 3 %) and a rare cause of hyperthyroidism, characterized by high levels of thyroid hormones in the presence of non-suppressed serum TSH concentrations. **Objective:** To describe the case of a patient with a non-suspected TSHoma with 15 years follow up. **Case Report:** A 33 year old woman with diagnosis of hypothyroidism after iodine -131 treatment at age of 18, complained to monitor hormone replacement. She reported a history of hyperthyroidism that went back to 1998 when started with typical symptoms. She was diagnosed with primary thyrotoxicosis and treated with methimazol for a brief period of time; finally received radio ablation in 1999. As TSH increased, substitutive administration of levothyroxine was early indicated. Levels of TSH never reached to normal, and remained constantly high together with normal high levels of T4 during the follow up (last profile in 2014 under levothyroxine 137 ug was TSH 9 T4L 1. 63). Among personal background, an incidental pituitary macroadenoma without supraselar extension was discovered in 2002, but wasn't linked to thyroid disease. We could obtain baseline thyroid profile: TSH: 3. 9 FT4: 6 T3: 289. Diagnosis of TSHoma is then reached. Pituitary images didn't show any change along the years. Evaluation of the rest of pituitary function was normal. Lanreotide Autogel 60 mg was indicated. TSH level dropped to 5.12 and 2.83 after the first and second injection respectively. **Conclusion:** TSHomas should be suspected in patients with high levels of thyroid hormones and non-suppressed serum TSH. An early and correct diagnosis avoids unnecessary thyroid ablation with permanent hypothyroidism and the risk of adenoma expansion.

Mirtha Guitelman is a speaker for Novartis and Sanofi Aventis. Florencia Lopez has no relationships to disclose.

P51

Personality, Coping Strategies and Pain Appraisal in Patients with Tumors of the Sellar Region With and Without Headache

Ilonka Kreitschmann-Andermahr[1], Georg Brabant[2], Michael Buchfelder[3], Renata Weber-Carneiro[3], Thomas Schenk[4], Sonja Siegel[1], [3]

[1]Department of Neurosurgery, University Hospital Essen, Germany; [2]Department of Experimental and Clinical Endocrinology, Med Clinic I - University of Luebeck, Germany; [3]Department of Neurosurgery, University Hospital Erlangen, Germany; [4]Department of Neurology, University Hospital Erlangen, Germany

Introduction: Headache is common in patients with tumors of the sellar region. Implicated causes include tumor size, cavernous sinus invasion and hormonal hypersecretion, but the interrelationships are far from proven. As in primary headache, it can be supposed that psychological factors play a role in headache of patients with sellar pathologies. Therefore, we investigated 112 patients with sellar tumors (predominantly pituitary adenomas) scheduled for neurosurgery for headache, personality structure, coping strategies and pain appraisal. **Methods:** Headache characteristics were assessed using the Migraine Disability Inventory (MIDAS) and the Essen Headache Inventory, administered via a hand-held palmtop device (software painDETECT®, Pfizer, Germany). Personality traits were explored via the NEO-FFI, coping strategies by the Brief Cope and pain appraisal using the Pain Catastrophizing Scale (PCS). All tools are self-assessment inventories. **Results:** 59/112 patients reported headache in the three months before surgery. On a scale of 1-100 mean pain intensity was 52.1 and 20.5% patients reported missing work time due to headache. Patients with headache experienced significantly more frequently catastrophizing thoughts, rumination and helplessness (PCS) and employed the coping strategies of "substance use" and "positive reframing" (Brief Cope) significantly more often ($p < 0.05$, respectively). Despite a lacking overall difference in personality traits between both groups, high scores on the neuroticism ($r = 0.370$; $p = 0.005$) and low scores on the extroversion subscale ($r = - 0.266$; $p = 0.046$) of the NEO-FFI correlated with significantly higher headache intensity on the MIDAS. **Conclusion:** We observed clear differences in psychological aspects between patients with sellar tumors with and without headache, corroborating findings in primary headache and other pain entities. Physicians involved in the treatment of sellar pathologies should be aware of the presence of such psychological factors in their patients with headache and defer from purely mechanistic causal attributions and therapies.

Acknowledgement: The study was supported in part with an unrestricted grant from Pfizer.

Michael Buchfelder receives honoraria, consulting fees and grants from Pfizer. The other authors have no relationships to disclose.

P52

Prevalence of Pituitary Adenomas at a Young University Hospital in Argentina

Sabate[1], MI; Battistone[2], MF; Rodriguez[2], A; Cavallo[2], A.

[1]Neuroendocrinology Section at Endocrinology Unit, Hospital Universitario Austral, Buenos Aires, Argentina; [2]Endocrinology Unit, Hospital Universitario Austral, Buenos Aires, Argentina

Context: data on pituitary adenoma (PA) prevalence are scarce. It contributes for the correct understanding of disease, needed health care resources and medical education at pre and postgrade level. **Objective:** The aim of our study was to evaluate epidemiological, biochemical and clinical features of pituitary adenomas at our neuroendocrinology section of our young University Hospital in Buenos Aires, Argentina in its first 13 years of life. **Methods:** Retrospective computerized review of 546 patients undergoing neuroendocrinology diagnosis at our hospital between 2000 at birth and June 2013 was performed. 269 patients presenting pituitary disease were evaluated at our neuroendocrinology section. 277 were excluded because of wrong diagnosis, pediatric age or not evaluation at endocrinology service. **Results:** 147 were pituitary adenomas (PA) and 122 were non PA selar pathology. After excluding 17 PA for insufficient data, 130 PA were analyzed. Mean age at time of the study of the population was 42,46 (range: 20-93) years, 103 were female and 27 male. The most common subtype of PA were prolactinomas (61,22%), followed by non-functioning adenomas (ANF) (16,33%), GH adenoma (6,80%), ACTH adenoma (3,40%) and thyrotropinoma (0,68%). 88 were microadenomas and 42 macroadenomas. Clinical features at diagnosis differed between each group, main signs and symptoms of prolactinomas: irregular menses, ANF: visual disturbances, GH adenomas: acral hypertrophy, ACTH adenomas: obesity and violaceous striae. **Conclusions:** Our study shows similar features of PA as the published in the literature. The institutional registry of PA and the knowledge of their epidemiological and clinical features in a young University center are important for the correct diagnosis in the shortest time, optimize use of economic resources and contribute to teaching strategies in a pre and postgrade medical institution.

The authors have no relationships to disclose.

PITUITARY FUNCTION

P53

A Novel Thymoma-associated Autoimmune Polyglandular Syndrome; Anti-PIT-1 Antibody Syndrome

Hironori Bando[1], Genzo Iguchi[1], Hidenori Fukuoka[1], Kenichi Yoshida[1], Ryusaku Matsumoto[1], Kentaro Suda[1], Hitoshi Nishizawa[1], Michiko Takahashi[1], Katsuyoshi Tojo[2], Wataru Ogawa[1], Yutaka Takahashi[1]

[1]Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan; [2]Division of Diabetes and Endocrinology, Department of Medicine, Jikei University School of Medicine, Tokyo, Japan

Recently, we have reported "anti-PIT-1 antibody syndrome" as a novel clinical entity exhibiting an acquired specific deficiency in GH, PRL, and TSH, in which autoimmunity to PIT-1 caused this syndrome (J Clin Invest 121 133 2011). This syndrome shows an autoimmune multiple endocrine organ involvement with various autoantibodies, indicating that it is categorized in autoimmune polyglandular syndrome (APS). As a mechanistic insight, we found PIT-1-reactive cytotoxic T cells (CTLs) in the peripheral leukocytes and the infiltration of CTLs in the involved tissues, strongly suggesting that CTL-mediated autoimmunity plays an important role in the development of this syndrome and anti-PIT-1 antibody itself is not a cause but a marker of this syndrome (JCEM 99 E1744 2014).

Intriguingly, we recently found thymomas in two of three patients with anti-PIT-1 antibody syndrome (under-investigation in the third patient). The thymoma was diagnosed with B2 type (WHO classification), which is closely associated with the pathogenesis of the autoimmune diseases such as myasthenia gravis (MG) and pure red cell anemia. Several mechanisms including the aberrant antigen expression and abnormalities in positive and negative selection of T cells have been implicated in the involvement of autoimmunity associated with thymoma.

We analyzed the titer of anti-PIT-1 antibody in the serum after the surgical resection of thymoma in the patient with anti-PIT-1 antibody syndrome and found that the titer decreased 8 months after the resection. These results indicate that anti-PIT-1 antibody syndrome is associated with thymoma and the thymoma may play a causal role in the development of this syndrome. The involvement of thymoma demonstrates a novel aspect in the pathogenesis of anti-PIT-1 antibody syndrome.

The authors have no relationships to disclose.

P54

Anterior Pituitary Dysfunction in Military Veterans with Mild Traumatic Brain Injury (MTBI): A Pilot Study

Shah KK[1], Joven M[2], Tarasova V[2], Saiprasad S[1, 2], Flor S[1], Anderson RJ[1, 2]

[1]Section of Endocrinology, Veterans Affairs (VA)-Nebraska Western Iowa Healthcare System, Omaha, NE, USA; [2]Division of Endocrinology, CHI Health, Creighton University Medical Center, Omaha, NE, USA

Objective: Traumatic brain injury (TBI) is a recognized cause of growth hormone deficiency (GHD), however, most studies have included civilian populations with varying degrees of TBI. Our aim was to evaluate the prevalence of GHD and other pituitary deficiencies following mTBI in Veterans. **Methods:** This single-center, prospective study was approved by our VA IRB. Endocrine evaluation included glucagon stimulation (GST, GHD≤3ng/dL), ACTH stimulation test (abnormal:cortisol<18mcg/dL), IGF-1, FT4, TSH, and total testosterone. Statistical analyses were done with the Mann-Whitney test with significance at p<0.05. **Results:** Twenty-four patients (males=20, females=4) are currently enrolled. Mean age and BMI (±SD) of the group were 30.8±6.41 years and 29.4±7.03, respectively. Thirteen patients (54.2%) had blast injury. Mean time from injury was 45.4 months. Secondary hypogonadism was found in 7/21 patients (33.3%) (Estradiol<15pg/mL; Total testosterone<300ng/dL). There was no evidence of central hypothyroidism or overt secondary adrenal insufficiency. Seventeen patients underwent GST. Six patients (5 males, 1 female) had GHD (35%). Mean age and BMI of the GHD group were 32.33±5.88 years and 35.23±7.89, respectively. Mean duration from injury was 58.5±45.1 months and 50% had blast injury. IGF-1 levels and age-adjusted SDS scores were normal. Compared with the GH-sufficient group, the GHD group had significantly lower mean AM cortisol level (p=0.002) and lower mean ACTH (p=0.04), although the basal values were normal in all patients. One patient in each group had lower cortisols after ACTH stimulation at 17.7 and 16.4mcg/dL, respectively; both had normal AM cortisols and peak GST cortisols (>9.1mcg/dL). Three patients in the GHD group had hypogonadism. No significant differences were found in mean BMI, IGF-1, time from injury, and baseline GH. **Conclusion:** Our pilot study indicates a high prevalence of GHD and secondary hypogonadism in Veterans with mTBI. The results support the consideration of a comprehensive endocrine evaluation in these patients.

The authors have no relationships to disclose.

P55

Case of Diabetes Insipidus (DI), Cerebral Salt Wasting (CSW) and Hypodipsic Hypernatremia

Lauren Labyer and Jonea Lim

University of Oklahoma Health Science Center, Department of Internal Medicine, Section of Endocrinology, Diabetes and Metabolism, Norman, OK, USA

Objective: Describe a case of 60 yo woman with DI, CSW and hypodipsic hypernatremia after aneurysm clipping of left anterior communication artery (ACA). **Case:** Post-op day (POD) 1, obtunded with polyuria (424 cc/hr). CT head no acute process. Serum sodium (Na) 159 mEq/L; serum osmolality 314 mOsmo/kg; urine osmolality 91 mOsmo/kg Fluid deficit was > 6 L. Desmopressin (DDAVP) 1 mcg IV reduced polyuria (46 cc/hr) & raised urine osmolality (655 mOsmo/kg). She was on DDAVP 0.5 mcg IV q.d. for 6 days. CT head POD 4 showed acute ACA territory infarct. She opens eyes to name. POD 8, serum Na dropped (124 mEq/L), urine Na 150 mEq/L, urine osmolality 571 mOsmo/kg. Clinical interpretation of volume status was difficult. Urine Output (UO) was 109 ml/hr. Blood pressure 91-171/61-70 mmHg. No edema. eGFR > 100 ml/hr. Cortisol and thyroid function were normal. Negative fluid balance (-1.2 L) achieved with fluid restriction. Hematocrit showed hemoconcentration. Serum Na nadir at 121 mEq/L. She stopped opening eyes to name. IV 3%NaCl initiated. Serum Na reached 132 mEq/L. She became alert, oriented, and able to follow all commands. POD 12, hypernatremia recurred (155 mEq/L), serum osmolality 321 mOsm/kg, urine osmolality 413 mOsmo/kg. UO was normal (112 cc/hr). Free water started. POD 14, Serum Na 153 mEq/L, UO 252 cc/hr, urine osmolality 260 mOsmo/kg. She had no thirst reflex. With DDAVP and scheduled oral water intake, normonatremia restored with normalization of UO. **Discussion:** Impaired thirst arousal from lesions to the hypothalamic osmoreceptors presents as hypodipsic DI. Hypertonic saline infusion improving serum Na and clinical status in hyponatremic patients managed as SIADH retrospectively may be to CSW. **Conclusion:** Awareness needed for hypodispsic DI. CSW vs SIADH in neurosurgical patients can be challenging.

The authors have no relationships to disclose.

P56

Chronic Hypopituitarism After Blast-related Concussion: Prevalence and Posttraumatic Symptomatology

Holly K. Rau[1], Elizabeth A. Colasurdo[2], Carl Sikkema[2], Sean P. Meichle[1], Daniel K. Morelli[1], Madeleine L. Werhane[3], Arundhati Undurti[4], Jane B. Shofer[4], Kathleen F. Pagulayan[1,4], Elaine R. Peskind[1,4], Charles W. Wilkinson[2,4]

VA Northwest Network Mental Illness Research, Education and Clinic Center, VA Puget Sound Health Care System, Seattle, WA, USA[1], Geriatric Research, Education and Clinical Center, VA Puget Sound Health Care System, Seattle, WA, USA[2], Joint Doctoral Program in Clinical Psychology, University of California, San Diego/San Diego State University, San Diego, CA, USA[3], Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, USA[4]

Introduction: Concussion (or mild traumatic brain injury (mTBI)) resulting from explosive blasts is the most common injury sustained by U.S. troops in Iraq and Afghanistan conflicts (OEF/OIF/OND), yet little is known about the consequences of mTBI on post-deployment quality of life. Further complicating this clinical picture is the high rate of chronic posttraumatic hypopituitarism (PTHP) following blast-related concussion. **Methods:** Prevalence and clinical presentation of PTHP and posttraumatic symptomology (PTS) was examined in two groups of OEF/OIF/OND Veterans: 13 who experienced blast-related concussion during deployment (mTBI), and 11 non-blast-exposed deployment controls (DC). PTHP screening involved measuring basal morning concentrations of 11 pituitary and target-organ hormones and administration of the glucagon stimulation test to evaluate capability for growth hormone and ACTH secretion. PTS was assessed using measures of depression, sleep, and PTSD symptoms; PTSD diagnosis was assessed using the CAPS. The VAPSHCS IRB approved all experiments. **Results:** In this sample, 38% of mTBI Veterans screened positively for PTHP. mTBI Veterans with PTHP (mTBI+PTHP, n=5) and without PTHP (mTBI-PTHP, n=8) reported similarly clinically-elevated levels of depressed mood, sleep disturbance, and traumatic symptoms. However, only one of the mTBI+PTHP participants met clinical criteria for PTSD, compared to 66% in the mTBI-PTHP group. Item-level analysis revealed that mTBI+PTHP endorsed decreased severity on avoidance items and increased severity on irritability items. These findings suggest that certain characteristic features of PTSD may be more or less prevalent in mTBI Veterans with PTHP. **Conclusions:** This study provides additional support for a high prevalence of PTHP following mTBI, as well as increased prevalence of PTSD, although most Veterans exhibiting PTHP did not meet diagnostic criteria for PTSD. Analysis of item-level responses to trauma-related questions indicates that decreased avoidance in PTSD may explain this difference. Attention to symptom reporting profiles may aid clinical differentiation of PTSD from PTHP.

The authors have no relationships to disclose.

P57

Gonadotroph Adenoma in Klinefelter's Syndrome

G. Gonca Oruk[1], M. Apaydın[2], N. Yüceer[3], H Yılmaz[1], A. Olmezoğlu[4]

[1]Department of Endocrinology and Metabolism; [2]Department of Radiodiagnostics; [3]Department of Neurosurgery; [4]Department of Radiation Oncology, Izmir Katip Celebi University Ataturk Training and Research Hospital, Izmir, Turkey

Klinefelter's syndrome (KS) is the most frequent sex chromosome aberration in males. The presence of a gonadotroph adenoma in the context of KS has been rarely confirmed. We report the case of a male with hypogonadism due to KS and a gonadotropin producing pituitary adenoma with increased serum levels of FSH and LH. A 17-yr-old white male was admitted to our outpatient clinic for evaluation of a pituitary tumor, found incidentally when an MRI was performed for headache .Physical examination revealed a tall male with abnormal skeletal proportions, poor virilization, intellectual deficiency. The MRI performed before the admission showed a suprasellar tumor of 11 mm diameter located on the left side. The endocrine investigation showed persistently high serum levels of both FSH (57.41, 48.98, 61.52 mIU/mL) and LH (43.92, 31.86, 44.37 mIU/mL) and low testosterone (1.65, 2.5, 4.5 ng/mL). The diagnosis of KS was confirmed by the karyotype analysis which revealed the classic 47, XXY karyotype. The patient was administered 50 mg/day of testosterone transdermally, free testosterone increased into the normal range, but FSH and LH did not return to normal and the size of the pituitary adenoma remained the same. The tumor was removed by transsphenoidal approach. One month after the operation both FSH (26.6 mIU/mL) and LH (20.2 mIU/mL) were decreased, however, still higher than normal. The physical examination revealed more hair in the facial, axillary and pubic areas. He started shaving twice weekly, improved sexual function and muscle strength since surgery. In conclusion, protracted stimulation of gonadotrophs due to lack of androgen feedback might be a factor in the formation of the gonadotroph adenoma and pituitary in patients with KS should also be evaluated in detail.

The authors have no relationships to disclose.

P58
Predictors of Central Diabetes Insipidus After Transsphenoidal Surgery

Erin A. Crocker[1], Timothy R. Smith[2], Rie Maurer[3], David J. Cote[2], Matthew Vestal[2], M. Maher Hulou[2], Kaitlin James[2], Kevin T. Huang[2], Wenya Linda Bi[2], Ian F. Dunn[2], Edward R. Laws[2], Whitney W. Woodmansee[1]

[1]Department of Endocrinology, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA; [2]Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [3]Center for Clinical Investigation, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA

Introduction: Transient (tDI) and permanent diabetes insipidus (pDI) are known complications of transsphenoidal surgery. This study aimed to investigate the endocrine and surgical predictors of postoperative DI. **Methods:** A retrospective review of 520 adult patients who underwent transsphenoidal surgery between 2008-2014 at Brigham and Women's Hospital was performed to investigate predictive factors and prevalence of DI. **Results:** 520 patients (278 women, 53.5%) were included in the analysis (mean age 48 years [SD ±15.4]). The majority presented with macroadenomas (79.2%). Pathologies included non-functional adenoma (40.8%), acromegaly (16.2%), prolactinoma (11.1%), Cushing's disease (10.3%), Rathke's cleft cyst (7.6%), and craniopharyngioma (2.2%). 111 patients had pre- or postoperative DI. Seventeen (3.3%) patients presented with DI preoperatively. The overall prevalence of postoperative DI was 18.1% (n=94): 92 (17.7%) patients developed tDI, and 10 (1.9%) progressed to/developed pDI. A significantly lower proportion of the postoperative DI cohort was on preoperative thyroid hormone (20.5%, p=0.0406), however, there was no trend in preoperative testosterone (5.8%, p=0.9437), glucocorticoid (10.7%, p=0.9713), or oral contraceptive use (3.3%, p=0.2331). Patients with postoperative DI were younger (p<0.0001), more likely to have microadenomas (p=0.0311), and had lower preoperative fasting glucose (p=0.0453) and HbA1c levels (p=0.0097) compared to those without DI. A lower proportion of DI patients had a history of CAD (0% vs. 4.6%, p=0.0321) or used preoperative lipid lowering agents (14.9% vs. 25.9%, p=0.0238) compared to non-DI patients. Surgical approach [microscopic (p=0.7979), endoscopic (p=0.9727), or combined (p=0.9172)] was not associated with DI prevalence. A higher proportion of postoperative DI patients experienced intra-operative CSF leaks (40.2%, p=0.0002), and lumbar drain placement (5.3%, p=0.0395). **Conclusion:** Although central DI is relatively common following transsphenoidal surgery, it is usually transient. Preoperative anterior pituitary hormonal replacement therapy was not associated with increased risk of DI. Postoperative DI was associated with tumor size (micro), but not surgical approach.

The authors have no relationships to disclose.

P59
Proteome Map of Adult Human Pituitary Glands

Kanchan Kumar Mukherjee[1], Soujanya D. Yelamanchi[2], Pinaki Dutta[3], Marta Korbonits[4], Bishan Das Radotra[5], Akhilesh Pandey[6], Harsha Gowda[2], S. K. Shankar[7], Anita Mahadevan[7], T. S. Keshava Prasad[2]

[1]Department of Neurosurgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [2]Institute of Bioinformatics, International Technology Park, Bangalore, India; [3]Department of Endocrinology, Postgraduate Institute of Medical Education & Research, Chandigarh, India; [4]Department of Endocrinology, Barts and the London School of Medicine, Queen Mary University of London, London, UK; [5]Department of Histopathology, Postgraduate Institute of Medical Education & Research, Chandigarh, India; [6]McKusick-Nathans Institute of Genetic Medicine and Departments of Biological Chemistry, Pathology and Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [7]Human Brain Tissue Repository, Neurobiology Research Centre, National Institute of Mental Health and Neuro Sciences, Bangalore, India

Objective: To carry out systematic proteomic profiling of adenohypophysis and neurohypophysis from human pituitary glands using high-resolution mass spectrometry. **Methods:** Adenohypophysis and neurohypophysis tissues were obtained from road accident subjects at the time of autopsy after ethical clearance was obtained from the Institute. Protein extraction and fractionation at the protein level and peptide level were carried out separately for both the tissues and the fractions were analyzed on a Fourier transform mass spectrometer. The LC-MS/MS data was searched against NCBI Human RefSeq 65 database using SEQUEST and Mascot search algorithms. Biological processes and molecular functions were acquired from Human Protein Reference Database. Pathway analysis was performed using GeneSpring software. **Results:** A total of 2,681 proteins were identified from the adult human pituitary glands, out of which 1,141 were never reported earlier. The 2,681 comprised of 2,026 proteins from the adenohypophysis and 2,089 proteins from the neurohypophysis. While 1,434 proteins were identified from both the tissues, 592 and 655 proteins were identified exclusively from the adenohypophysis and neurohypophysis tissues, respectively. GO analysis of the pituitary proteins identified in this study revealed that they were associated with biological processes such as apoptosis, regulation of cell cycle, cell adhesion, translation and protein folding. Pathway analysis of the unique proteins identified in this study resulted in the enrichment of proteins corresponding to KEAP1-NRF2 and neurotrophin signaling pathways. **Discussion:** In this study, we have reported 1,141 additional proteins for the first time from the human pituitary glands. This data will serve as a vital resource for the further investigations on the physiological role of pituitary glands and the proteins secreted by them. We anticipate that the identification of several unique and novel proteins identified in this study will accelerate biomedical research to decipher their role in the functioning of pituitary glands and associated human diseases.

The authors have no relationships to disclose.

P60

Surgeon Volume and Geography Impact Cost of Care for Pituitary Tumor Surgery

Charles C. Lee[1], Amy Lalonde[2], Matthew C. Miller[3], Laura Calvi[4], Peter Salzman[5], G. Edward Vates[6]

Department of Neurosurgery[1,6]; Department of Biostatistics and Computational Biology[2,5]; Department of Otolaryngology[3]; Division of Endocrinology, Diabetes, and Metabolism[4], University of Rochester Medical Center, Rochester, NY, USA

Introduction: High cost care does not necessarily provide better care. We examined the impact of surgeon volume and geography on hospital costs, charges, & length of stay (LOS) across New York State for a small, well-defined population of patients undergoing transsphenoidal pituitary tumor surgery. **Methods:** Using the Healthcare Cost and Utilization Project State Inpatient Database for NY, we performed cost analysis on pituitary tumor surgery (2008 to 2012). All patients underwent elective surgery and were discharged to home or self-care. Surgeon volume was dichotomized into low-volume surgeons (SV < 20) and high-volume surgeons (SV > 20). NY was divided into two regions: Upstate and Downstate. Comparisons were made between surgeon volume groups and regions on hospital charges, costs, and length of stay. **Results:** 2,240 surgeries were performed in NY (2008-2012). High-volume surgeons performed 1,269 (56.7%) surgeries. Patient mean age was 50.7 years (53% female).

Initial Charges on Day 1		
	Downstate	Upstate
SV > 20	$15,870	$14,141
SV < 20	$31,961	$26,628
Daily Charges for every extra day in the hospital		
	Downstate	Upstate
SV > 20	$11,052	$2,482
SV < 20	$9,025	$2,950
Initial Costs on Day 1		
	Downstate	Upstate
SV > 20	$5,819	$7,012
SV < 20	$9,741	$9,447
Daily Costs for every extra day in the hospital		
	Downstate	Upstate
SV > 20	$3,450	$1,331
SV < 20	$2,738	$1,523

High-volume surgeons had lower initial charges and costs compared to low-volume surgeons regardless of geographic region. Conversely, additional daily charges were much lower in Upstate NY compared to Downstate, regardless of surgeon volume. Median LOS for high-volume surgeons and low-volume surgeons were 2 and 3 days. All of these relationships were statistically significant. **Conclusion:** Our analysis demonstrates that within New York, high-volume pituitary neurosurgeons in Upstate had decreased hospital charges, costs, and length of stay the most. These data suggests that patients with pituitary tumors (a highly portable disease) should be considered for referral to high volume surgeons to promote high value, cost-effective care.

The authors have no relationships to disclose.

P61

The Thickened Pituitary Stalk with Papillary Carcinoma of the Thyroid: A Diagnostic Conundrum

Michael S. Gordon[1]; Murray B. Gordon[2]

[1]Division of Endocrinology, Diabetes & Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [2]Division of Endocrinology, Allegheny Neuroendocrinology Center, Allegheny General Hospital, Drexel University College of Medicine, Pittsburgh, PA, USA

Etiologies of a thickened stalk include inflammatory, neoplastic and idiopathic origins, and the underlying diagnosis may remain occult or be a diagnosis of exclusion. We report a case of a patient with a thickened pituitary stalk (TPS) and papillary thyroid carcinoma (PTC) whose diagnosis remained obscure until a skin lesion appeared.

The patient presented with PTC, status post thyroidectomy and I131 therapy. She had a 5 year history of polyuria/polydipsia. Overnight dehydration study confirmed diabetes insipidus; 24hr urine volume was 12.1 liters. Polydipsia and polyuria responded to DDAVP nasal spray. MRI revealed TPS with loss of posterior pituitary bright spot. Evaluation showed hypogonadotropic hypogonadism (E2 17 pg/ml, LH 0.7, FSH 1.2 mIU/ml) and IGF-1 34 ng/dl (SDS -3.2). Chest x-ray and ACE levels were normal. Long bone and skull x-rays to evaluate for extra pituitary sites of Langerhans Cell Histiocytosis (LCH) were unremarkable. Evaluation for a germinoma negative: normal serum and CSF beta- hCG, alpha-fetoprotein and CEA. Three years later, the patient developed vulvar labial lesions that responded to courses of oral prednisone. Initial biopsy showed acute and chronic inflammation and repeat biopsy after spread to the inguinal region was consistent with LCH. She was treated with high dose prednisone with improvement in TPS and skin. This case illustrates that one must be vigilant for extra-pituitary manifestations of systemic diseases to diagnose the etiology of TPS. An activating mutation of the proto-oncogene BRAF is a potential unifying etiology of both PTC and LCH.

The authors have no relationships to disclose.

PROLACTIN/PROLACTINOMA

P62

Cabergoline Induces Autophagic Cell Death of Rat Pituitary Tumor Cells by Blocking Autophagic Flux

Zhe Bao Wu[1]; Jiao Tong[2]

[1]Department of Neurosurgery, Ruijin Hospital, Shanghai; [2]University School of Medicine, Shanghai, China

Objective: Cabergoline (CAB), the first-line drug for treatment of prolactinomas, is effective in suppressing prolactin hypersecretion, reducing tumor size, and restoring gonadal function. However, mechanisms for CAB-mediated tumor shrinkage are largely unknown. **Methods:** To analyze the function of CAB, rat MMQ and GH3 pituitary cell lines were utilized. Autophagic level was evaluated by GFP-LC3, transmission electron microscopy, and confocal microscope. Expression of autophagic-related protein was analyzed by western blot. Cell death was measured by flow cytometry, CCK8 and ATP assay. To clarify the precise role of autophagy on CAB-mediated cell death, we did in vitro analysis with small interfering RNAs and chemical inhibitors. **Results:** CAB induces autophagosome formation in MMQ and GH3 cells at the early stage through inhibiting mTOR pathway, showing higher conversion rates of LC3-I to LC3-II, GFP-LC3 aggregation, and increased autophagosome formation. Interestingly, CAB treatment augmented lysosome acidification and resulted in impaired proteolytic degradation within autolysosomes, thus blocking the autophagic flux, leading to the accumulation of p62 aggregation and undigested autophagosomes. Knochdown of ATG7, ATG5, and Becn1, as well as chemical inhibition of autophagy, can significantly rescue the CAB-mediated cell death of MMQ cells ($p<0.05$). **Conclusions:** Our study provides evidence that CAB concomitantly induces autophagy and inhibits the autophagic flux, leading to accumulation of undigested autophagosomes and/or autolysosomes that ultimately result in cell death. These findings elucidate novel mechanisms for CAB action and provide a new therapeutic strategy for the medical management of pituitary tumors.

The authors have no relationships to disclose.

P63

Low Estrogen Receptor Alpha Expression is Associated with Male Gender and Poor Prognosis in Prolactin Tumors

Etienne Delgrange[1], Anne Wierinckx[2, 3], Alexandre Vasiljevic[2, 4, 5], Patrick François[6], Emmanuel Jouanneau[2, 4, 7], Gérald Raverot[2, 4, 8], Jacqueline Trouillas[2, 4, 5]

[1]Service d'Endocrinologie, CHU Dinant-Godinne UCL Namur, Université Catholique de Louvain, Namur, Belgium; [2]Université de Lyon 1, Lyon, France; [3]Centre de Recherche en Cancérologie de Lyon, Lyon, France; [4]Centre de Neurosciences de Lyon, Lyon, France; [5]Centre de Pathologie Est, Hospices Civils de Lyon, Groupement Hospitalier Est, Bron, France; [6]Service de Neurochirurgie, Hôpital Bretonneau, Université François Rabelais, Tours, France; [7]Service de Neurochirurgie, Hospices Civils de Lyon, Groupement Hospitalier Est, Bron, France; [8]Fédération d'Endocrinologie, Hospices Civils de Lyon, Groupement Hospitalier Est, Bron, France

Context: A gender difference in progression of prolactin (PRL) tumors has been disputed for years. **Objective:** To compare tumor characteristics and postoperative clinical course between men and women, and correlate data to estrogen receptor α (ESR1) expression status. **Design:** Eighty-nine patients (59 women and 30 men) operated on for a PRL tumor and followed for at least 5 years were selected. Tumors were classified into 5 grades according to their size, invasion and proliferation characteristics. The ESR1 expression was detected by immunohistochemistry and a score (0-12) calculated as the product of the percentage of positive nuclei and the staining intensity. Molecular analyses were performed on fragments from 30 frozen tumors (10 women and 20 men). **Results:** We found a significant preponderance of high grade tumors among men ($p<0.0001$) and a lower surgical cure rate in men (23%) than in women (71%). Patients resistant to medical treatment were mainly men (7/8), 6 of whom showed tumor progression despite postoperative medical treatment which led to multiple therapies and eventually death in 3. For ESR1, a good correlation was found between protein expression detected by IHC and mRNA levels. The median score for ESR1 expression was 1 in men (range: 0-8) and 8 in women (range: 0-12) ($p<0.0001$). The expression of ESR1 was inversely correlated with tumor size ($r = -0.59$; $p<0.0001$) and proliferative activity. All dopamine agonist-resistant tumors and all grade 2b (invasive and proliferative) tumors (from 10 men and 4 women) were characterized by low ESR1 expression. Some estrogen-regulated genes such as insulin receptor substrate (IRS)-1 were down-regulated in ESR1 negative tumors. **Conclusions:** PRL tumors in men are characterized by lower ESR1 expression than in women, related to greater proliferative activity and resistance to treatment.

The authors have no relationships to disclose.

P64

Pituitary Dysfunction In The Acute, Subacute And Chronic Phases Of Traumatic Brain Injury (Tbi)

Godwin C. Ojieh[1], Osaretin A.T. Ebuehi[2], Friday K. Iweka[3]

[1]Department of Medical Biochemistry, College of Medicine, Ambrose Alli University, Ekpoma, Edo state, Nigeria; [2]Department of Biochemistry, College of Medicine, University of Lagos, Lagos, Nigeria; [3]Department of Medical Laboratory Science, College of Medicine, Ambrose Alli University, Ekpoma, Edo state, Nigeria

Background: TBI is a leading cause of premature death and disability for young adults worldwide. Screening for pituitary dysfunction is not performed post TBI period, and associated abnormalities often go undiagnosed and untreated. **Objective:** In light of the potentially adverse effects of hormonal deficits on the rate and extent of both physical and cognitive recovery, the pituitary target gland hormones are evaluated in the acute, subacute and chronic phases of TBI to proffer time related hormone replacement strategies. **Method:** 96 males and 57 nonpregnant, nonlactating and premenopausal females without history of chronic ailment were enrolled.In each case, blood samples were analyzed for testosterone, cortisol, oestradiol and prolactin within 24h, at first and sixth week of trauma. **Discussion:** 85 of the men with moderate to severe TBI had low mean testosterone and cortisol in the acute, subacute and chronic phases. The men with mild TBI had low testosterone in the acute and subacute phases which picked up to normal in the chronic phase. The patients had increased mean cortisol in the acute phase but normal in the subacute and chronic phases. 45 of the women with moderate to severe TBI had low mean oestradiol in the acute, subacute and chronic phases. The remaining patients with mild TBI had minimal lowering in the acute and subacute phases with regained normalcy in the chronic phase. Hyperprolactinaemia was present in the moderate to severe TBI. Those with mild TBI had average normal level. **Conclusion:** Moderate to severe TBI was found to be associated with abnormalities of testosterone, cortisol, oestradiol and prolactin secretions in the acute, subacute and chronic phases of TBI. Therefore, routine assessment is recommended in these phases of TBI for a more effective management and optimum patients recovery and improved quality of life.

The authors have no relationships to disclose.

P65

Pregnancies in Women Harboring Prolactinoma Treated with Cabergoline: Experience of a Single Center

Glezer A, Caccelli M, Bueno CBF, Sickler T, Bronstein MD

Neuroendocrine Unit, Division of Endocrinology and Metabolism, Hospital das Clinicas, University of Sao Paulo Medical School and Laboratory of Cellular and Molecular Endocrinology (LIM/25), University of Sao Paulo Medical School, Sao Paulo, Brazil

Prolactinoma is an important cause of hypogonadism/infertility and dopamine agonist drugs (DA) promote hormonal control and tumor volume decrease in more than 80% of the cases. As the reports of pregnancies induced by bromocriptine still are ten times higher than dose induced by cabergoline (CAB), the first stands as the drug of choice for women desiring pregnancy, to date. Most cases concern to patients harboring microadenomas and intrasselar macroprolactinomas, in whom DA usually should be withdrawal after pregnancy confirmation. Nevertheless, data regarding pregnancy induced by CAB is increasing. We described 20 pregnancies induced by CAB in 19 women harboring prolactinomas (8 micro, 11 macro). Mean age at pregnancy diagnosis: 33 yrs ,mean time of CAB use: 46.8 months. CAB mean dose was 1 mg/week being withdrawal at 6 weeks of pregnancy in most cases. Three patients harboring invasive macroprolactinomas were on CAB (0.5- 2 mg/w) during all pregnancy period. Additionally, CAB was reintroduced in other two patients due to tumor mass effect, being effectively in one case, the other one submitted to surgery. Three preterm births (36 and 37 weeks) and 14 births at term were observed; three of them presented low weight for gestational age. Children age currently varied between 4 months and 15 yrs. One preterm girl presented epilepsy and precocious puberty and another one presented hip dysplasia. All other 15 children had no abnormalities to date. After delivery, serum PRL levels ranged from 15.5 to 167ng/mL. All patients except three needed to reassume CAB treatment after finishing nursing, three of them needing a lower dose. Sellar imaging pointed to tumor disappearance (36%) or significant reduction (27%). In our sample, fetal complications seem to be higher than in the general population, in contrast to literature. Therefore, we need more data in order to compare CAB to bromocriptine safety profile.

The authors have no relationships to disclose.

P66

Second Attempt of Cabergoline Withdrawal in Patients with Prolactinomas After a Failed First Attempt: Is it Worthwhile?

Lucio Vilar[1],[2], José Luciano Albuquerque[1], Patricia S. Gadelha[1], Frederico Rangel Filho[1], Ruy Lyra[1]

[1]Division of Endocrinology, Hospital das Clinicas, Federal University of Pernambuco, Recife, Brazil; [2]Diabetes & Endocrinology Center of Pernambuco, Recife, Brazil

Background: Successful discontinuation of cabergoline (CAB) treatment has been reported in 31 to 74% of prolactinomas patients treated for at least two years. In contrast, it is not well established whether CAB therapy can be successfully withdrawn after a failed first attempt. This prospective open trial was designed to address this topic and to try to identify possible predictor factors. **Methods:** Among 180 patients with prolactinomas on CAB therapy, the authors selected those who fulfilled very strict criteria, particularly additional CAB therapy for at least 2 years, normalization of serum prolactin (PRL) levels following CAB restart, no tumor remnant > 10 mm, no previous pituitary radiotherapy or surgery; and current CAB dose ≤1.0 mg/week. Recurrence was defined as an increase of PRL levels above the upper limit of normal. **Results:** A total of 34 patients (70.6% female) treated with CAB for 24-30 months were recruited. Ten patients (29.4%) remained without evidence of recurrence after 24–26 months of follow-up. Twenty four patients (70.6%) recurred within 15 months (75% within 12 months) after drug withdrawal and ~80% were restarted CAB. Median time to recurrence was 10.5 months (range, 3–15). Despite overlapping values, non-recurring patients had significantly lower mean PRL levels before withdrawal. Moreover, the recurrence rate was lower in subjects without visible tumor on pituitary MRI than in those with small remnant tumor (60 vs. 79%), though the difference was not statistically significant (P= 0.20). No other characteristic could be identified as a predictor of successful CAB discontinuation. **Conclusion:** A second attempt of CAB withdrawal after 2 additional years of therapy may be successful, particularly in patients with lower PRL levels and no visible tumor on pituitary MRI. Close monitoring of PRL level is mandatory, especially within the first year after withdrawal, where most recurrences are detected.

The authors have no relationships to disclose.

P67

Single Center Surgical Experience in the Treatment of Prolactinomas

Donegan D.[1], Atkinson J.[2], Natt N.[1], Nippoldt T.[1], Jentoft M.[3], Meyer F.[2], Erickson D.[1]

[1]Department of Endocrinology, [2]Department of Neurosurgery, [3]Department of Anatomic Pathology, Mayo Clinic, Rochester, MN, USA

Background: Prolactinomas are the most common pituitary tumors and primarily treated with medical therapy. Given the efficacy of dopamine agonists (DA), surgery has remained a second line treatment option. However some tumors display resistance and or patients maybe intolerant of DA resulting in a need for alternative treatment options. We examined the indications, efficacy and safety of surgery for the treatment of prolactinomas. **Methods:** Following IRB approval, we performed a retrospective analysis of all patients who had surgery for a prolactinoma at the Mayo Clinic from January 1993 to November 2014. **Results:** Eighty patients (32 males, 48 females median age 29 years) were analyzed. The most common indications for surgery were treatment resistance to DA in 27 (33.75%) followed by medication intolerance in 19 (23.75%) and patient preference in 15 (18.75%) patients (other indications n= 19). DA therapy had been trialed prior to surgery in 59 (74%) patients with a median duration of 11 months (0.1-120 months). Macroprolactinomas accounted for 64% (n= 51) of tumors with cavernous sinus invasion present in 24% of tumors (macro= 17, micro= 2). Following surgery 34 (43%) patients were in remission (no treatment and normal prolactin); of these 12 were macroadenomas, 2 with cavernous sinus invasion; and 22 microadenomas. Persistent disease (elevated prolactin or requiring DA) was seen in 37 (47%) patients. Recurrence occurred in 8 (10%) cases. Following surgery 39 of 57 (68%) patients on DA preoperatively no longer required treatment. Postoperative complications included 7 transient and 4 permanent cases of diabetes insipidus, CSF leak in 6, meningitis in 1 and new permanent pituitary hormone deficiencies in 11 patients. **Conclusion:** Surgery for prolactinomas, although second line given the risk of complications, can result in a complete remission in 43% of patients (rate for microprolactinomas 76%) and cessation of medical therapy in 68% of patients.

The authors have no relationships to disclose.

REPRODUCTIVE

P68

Functional Gonadotroph Adenomas: A Case Series of Four Patients

David J. Cote[1], Timothy R. Smith[1], Courtney N. Sandler[2], Tina Gupta[2], Tejus Bale[3], Ian F. Dunn[1], Umberto De Girolami[3], Whitney W. Woodmansee[2], Ursula B. Kaiser[2], Edward R. Laws[1]

Departments of Neurosurgery[1], Endocrinology, Diabetes, and Hypertension[2], and Pathology[3], Brigham and Women's Hospital, Boston, MA, USA

Objective: The objective of our study is to advance clinical understanding of functional gonadotroph adenomas (FGA). **Introduction:** FGA are rare tumors of the pituitary gland that secrete biologically active gonadotropins and can lead to significant morbidity. We report four cases of FGA with focus on presentation, diagnosis, operative treatment, and outcomes. **Methods:** We performed a retrospective review of adult patients who underwent transsphenoidal resection at a high-volume, quaternary-care academic center from August 1997 to October 2014 (n=1378) to identify patients who had pathologic and biochemical confirmation of FGA with either non-suppressed LH/FSH in the setting of elevated gonadal steroids, clinical symptoms, or both. **Results:** FGA was documented in four patients (two men, two women) over a 17-year period. All patients had macroadenomas. Presentations included visual field deficits in three patients, headache and sexual dysfunction in two, and ovarian cysts in both women. One patient presented with infertility. Two patients presented with elevated serum FSH, and two presented with non-suppressed FSH/LH despite elevated gonadal steroids. Each patient received a thorough endocrine evaluation followed by an endonasal transsphenoidal operation for lesional resection. Immunohistochemical analysis of tumor samples stained positively for FSH and LH in three patients, and LH exclusively in one patient. Subsequent follow up (median= 8 months, range= 4-64 months) indicated remission in all patients (one requiring re-operation, one requiring radiation), with a return to normal physiologic levels of FSH and LH. **Conclusions:** FGA are extremely rare and can be diagnostically and therapeutically challenging. They often present late as macroadenomas with significant morbidity due to non-specific symptoms. FGA must be considered as a potential diagnosis in patients harboring pituitary adenomas with reproductive dysfunction, and transsphenoidal resection should be the initial treatment of choice. Resection can reduce endocrine dysfunction, resolve headaches, improve impaired vision, and provide tissue for detailed analysis.

The authors have no relationships to disclose.

P69

Neuro-ophthalmologic Complication of a Nonfunctioning Adenoma During Pregnancy

Di Paolo, Maria Victoria, Rosmino, Josefina, Guitelman, Mirtha Adriana

Endocrinology Division , Hospital Carlos G Durand, Buenos Aires, Argentina

Introduction: Eighty percent of non-functioning adenomas (NFA) are gonadotropin secreting macroadenomas. The usual clinical presentation is symptoms of mass effect and hypopituitarism in middle age patients. It is a rare condition in young women and as a complication during pregnancy. **Objective:** The exceptional finding of a NFA as a complication during pregnancy. **Case Report:** A 38 year old woman was referred at 32nd week of spontaneous pregnancy because of progressive visual loss during the previous two months. MRI revealed a pituitary lesion, with suprasellar extension and compression of optic chiasm. Computerized Visual Field showed a right amaurosis and left temporal hemianopsia. Hormonal deficit and hypersecretion was ruled out. Prolactin levels were high as expected. Dopamine agonists and corticosteroids were started. She developed diplopia and severe headache, so pregnancy was interrupted at 34th week. After a non complicated delivery of a normal new born, transphenoidal surgery was performed, she recovered visual field and menstrual cycles, and remained with normal pituitary function. The pathology was consistent with typical pituitary FSH and LH producing adenoma. During the follow up pituitary MRI showed a small tumor rest, which remained without changes after 6 months. **Conclusion:** Gonadotropinomas are unusual complicated tumors during pregnancy, being prolactinomas and hypophysitis more common. There are few data in the literature making it an exceptional case, and can contribute with new diagnoses in pituitary pathology during pregnancy.

Mirtha Guitelman is a speaker for Novartis and Sanofi Aventis. The other authors have no relationships to disclose.

TUMORS

P70

ACTH-secreting Pituitary Adenomas: What Role for PRKCD?

Gentilin E[1],[2], Gagliano T[1], Benfini K[1], Carmelina di Pasquale[1], Maria Rosaria Ambrosio[1], Simona Falletta[1], degli Uberti E[1], [2], Zatelli MC[1], [2]

[1]Section of Endocrinology and Internal Medicine, Dept. of Medical Sciences, University of Ferrara, Italy; [2]Laboratorio in rete del Tecnopolo "Tecnologie delle terapie avanzate" (LTTA) of the University of Ferrara, Italy

The mechanisms underlying the pathogenesis of adrecorticotroph hormone (ACTH) secreting pituitary adenomas is a matter of great interest, since clinical effects of uncontrolled hypercortisolism are very grim and are associated with high morbidity and mortality. Pituitary surgery is always referred to as the first-line therapy, but is burdened with a high recurrence/persistence rate. The goal of current research is not only to identify new effective drugs but also to explore novel mechanisms that may represent innovative pharmacological targets. Recently, Protein Kinase C Delta (PRKCD) has been highlighted among the pathways that are disrupted in ACTH-secreting pituitary adenomas. PRKCD is a serine-threonine kinase that regulates various physiological processes like proliferation, cell cycle, differentiation and apoptosis. Recently, we demonstrated that PRKCD is expressed at low level in human ACTH-secreting pituitary adenomas and that it powerfully controls cell cycle in vitro.

We therefore set out to investigate whether PRKCD silencing could affect the behaviour of the murine ACTH-secreting pituitary adenoma cell line, AtT-20/D16v-F2 cells. Silencing of PRKCD silencing resulted in increased cell viability, altered morphology, and enhanced expression of EGF receptor, possibly indicating an aggressive behavior. We also found a negative correlation between EGFR expression levels and PRKCD expression levels in human ACTH-secreting pituitary adenomas, suggesting a mutual interplay between the two proteins. Our study suggests that PRKCD may be involved in pituitary neoplastic transformation and candidates this protein for future studies concerning novel therapeutic strategies.

The authors have no relationships to disclose.

P71
Adamantinomatous Craniopharyngioma Contains Senescent Cells with Tumour-Inducing Potential

Juan Pedro Martinez-Barbera

Developmental Biology and Cancer Programme, Institute of Child Health, University College London, UK

Adamantinomatous craniopharyngioma (ACP) is a paediatric pituitary tumour that is associated with high morbidity due to the tendency of the tumour to infiltrate locally into surrounding brain structures such as the hypothalamus and visual tracts. We have developed and validated two mouse models for human ACP, which have provided original insights into the aetiology and pathogenesis of human ACP. Recently, we revealed a novel and intriguing mechanism by which Sox2+ve pituitary stem cells contribute to oncogenesis, which is fundamentally different to the classical cancer stem cell paradigm. When targeted to express oncogenic beta-catenin, mutant Sox2+ve stem cells do not give rise to the progeny populating the tumour, instead these oncogenic stem cells induce tumorigenesis in a paracrine manner. To provide insights into this novel mechanism, we have revealed that in these models, senescence and the senescence-associated secretory phenotype are critical players for tumour progression. Specifically, we show that following a short burst of proliferation, oncogenic Sox2+ve cells stop dividing to form beta-catenin-accumulating cell clusters that become senescent. These clusters show senescence-associated beta-galactosidase activity, p53 pathway activation and up-regulate the expression of the cell cycle inhibitors p21 and p16. Additionally, cluster cells show elevated expression of lysosomal components and activate the autophagy pathway. Oncogenic beta-catenin also causes DNA damage as evidenced by an increase in H2A.X phosphorylation, triggering the DNA damage response. As a consequence, NF-κB signalling is elevated resulting in the expression of activation a Senescence-Associated Secretory Phenotype (SASP) with expression of multiple secreted factors including pro-inflammatory cytokines such as IL1, IL6 and IL8. Of translational significance, we show that this mechanism is relevant in human ACP tumorigenesis. Beta-catenin-accumulating cell clusters in human ACP express several senescence markers such as p21, p16 and lysosomal enzymes, exhibit DNA damage and activate P53, NF-κB and autophagy pathways, resulting in SASP activation. Together, the mouse and human data suggest that senescence and SASP are likely to modify the tumour microenvironment resulting in cell transformation, tumour growth and survival.

The author has no relationships to disclose.

P72
Hormonal Outcome of Transsphenoidal Surgery in Patients with Nonfunctioning Pituitary Adenoma: a Single Center Experience

Jung Hee Kim[1], Kyeong Seon Park[1], A Ram Hong[1], Hak Chul Jang[1], Yong Hwy Kim[2], Sang Wan Kim[1], Chan Soo Shin[1], Seong Yeon Kim[1]

[1]Department of Internal Medicine, [2]Department of Neurosurgery, Seoul National University College of Medicine, Seoul, South Korea

Hypopituitarism has been suggested as a surgical indication in patients with nonfunctioning pituitary adenoma (NFPA). However, transsphenoidal surgery carries both the risk of hormone loss and the benefit of hormone recovery. We aimed to evaluate the surgical outcome of transsphenoidal surgery in patients with NFPA in an aspect of hormone function.

We recruited patients with NFPA prospectively, who performed the combined pituitary dynamic test pre- and postoperatively and underwent the transsphenoidal surgery in Seoul National University Hospital from 2012 to 2013. Total 44 patients (17 men, 27 women) were included to assess the endocrine function

Of 44 patients, 21 patients (47.7%) with preoperative hormone deficiency improved hormone function, and 6 patients (13.6%) have resolved after surgery. The hormone functions in nine patients (20.5%) were aggravated, and new hypopituitarism occurred in 2 patients (4.5%). Of 13 patients with hyperprolactinemia due to stalk effect, 10 patients (76.9%) have experienced the recovery of hormone function, and 3 patients had the same hormone status ($p = 0.023$). TRH-stimulated TSH responders (n=37) was not related with postoperative hormone recovery. Tumor size was not related with the recovery of hormone function.

In conclusion, the recovery of hormone function occurred in 47.7% of patients with NFPA in our hospital. New hypopituitarism occurred only in 2 patients. Hyperprolactinemia was the predictor for the recovery of hormone function.

The authors have no relationships to disclose.

P73

Whole Exome Sequencing of FIPA Families Without AIP Mutations

Nara Sobreira[1], Michele Migliavacca[1], David Valle[1], Roberto Salvatori[2]

[1]Institute of Genetic Medicine; [2]Division of Endocrinology and Pituitary Center, Johns Hopkins University, Baltimore, MD, USA

INTRODUCTION: Familial clustering occurs in approximately 2% of pituitary adenomas. Familial Isolated Pituitary Adenoma (FIPA) syndrome is a condition in which adenomas cluster in a family without other endocrine neoplasia. It includes both homogeneous (same histology) and heterogeneous families. Daly et al. reported that in about 75% of FIPA individuals the relationship between affected members is of first degree (1). In that study, most families had 2-4 affected members, and FIPA individuals were diagnosed on average 4 yrs before patients with sporadic adenomas. To date, germline mutations in two genes have been associated to FIPA: mutations in the tumor suppressor AIP are present in approximately 20% of FIPA families, and recently a microduplication at chromosome Xq26.3 has been reported in a syndrome of early onset GH and prolactin hypersecretion, caused by a spectrum of pituitary pathology including mixed GH- and prolactin-secreting adenomas and hyperplasia (2). **METHODS:** Here we used whole exome sequencing to investigate the molecular basis of 6 unrelated FIPA families (5 heterogeneous and 1 homogeneous), each including at least two affected individuals with a pituitary adenoma and without AIP mutations. Using the Variant Analysis Tool of PhenoDB (3) we prioritized rare heterozygous or homozygous functional variants (missense, nonsense, splice site variants and indels), and 5' and 3' UTR variants in each of the 6 families, excluding variants with a MAF> 0.01 in the Exome Variant Server (release ESP6500SI-V2), or 1000 Genomes Project, or present in dbSNP 126, 129, and 131. We also excluded variants found in our in-house controls. Next, we asked what same genes where mutated in a subset of the 6 families. **RESULTS AND CONCLUSIONS:** The candidate genes identified are being further investigated to see if they map with the disease, and/or are likely to be involved based on known biology of the gene.

1) Daly A et al. *J Clin Endocrinol Metab.* 2006 91:3316-23
2) Trivellin G et al. *N Engl J Med.* 2014 Dec 3. [Epub ahead of print]
3) Hamosh A et al. *Hum Mutat.* 2013 34:566-71

The authors have no relationships to disclose.

Abstract Index by Title

ABSTRACT TITLE	Author	Poster #	PAGE
Effect of Treatment with Pegvisomant on Bone Mineral Density and Bone Markers in Patients with Acromegaly	Kuker, A.	25	55
Efficacy and Safety of LCI699, A Potent 11β-hydroxylase Inhibitor, in Patients with Cushing's Disease: A 22-week, Multicenter, Open-label Study	Pivonello, R.	Hot Topics	37
Efficacy and Safety of Retinoic Acid in Patients with Cushing's Disease: Results of a Prospective Study	Vilar, L.	12	48
Endoscopic Biopsies of Lesions Associated with a Thickened Pituitary Stalk	Yao, Y.	44	64
Evaluation of Bone Resistance Parameters in Active and Controlled Acromegaly and Matched Controls with Quantitative CT (QCT)	Valassi, E.	26	55
Evidence Based Guidelines in Acromegaly: Limitations and Utility	Trainer, P.	Invited Lecture	12
Evidence-Based Guidelines in Acromegaly: Limitations and Utility	Gadelha, M.	Invited Lecture	11
Expanded Endonasal Endoscopic Approach for Selective Adenomectomy in Cushing's Disease: 7-Year Experience of a Single Surgical Team	Gallia, G.	13	49
Experience of Bilateral Inferior Petrosal Sinus Sampling with DDAVP Stimulation Test in the Diagnosis of 275 Cases with the Cushing's Syndrome in a Single Center	Lu, L.	14	49
Expert Consensus for Surgical Treatment of Pituitary Adenoma in China	Wang, R.	48	66
Expression and Correlation of Gsp Oncogene, PKCδ and ERK1/2 in Human Somatotrophinomas	Chen, X.	27	56
Extended Transsphenoidal Approach for Pituitary Adenomas Invading the Cavernous Sinus Assisted by Multiple Techniques	Bao, X.	49	66
Functional Gonadotroph Adenomas: A Case Series of Four Patients	Cote, D.	68	76
GH as a Metabolic Hormone	Kineman, R.	Invited Lecture	8
GH Regulation of Electrolyte Balance	Kamenický, P.	Invited Lecture	14
GH-Induced Signaling in Human Muscle	Jørgensen, J.	Invited Lecture	14
Gigantism: Detailed Clinical Characteristization of a Single Center Series	Singhal, V.	28	56
Glucose and Lipid Levels After Lanreotide Autogel/Depot (LAN) 120mg in Treatment-naïve Patients with Acromegaly: Data from the PRIMARYS Study	Petersenn, S.	29	57
Gonadotroph Adenoma In Klinefelter's Syndrome	Oruk, G.	57	70
Hormonal Outcome of Transsphenoidal Surgery in Patients with Nonfunctioning Pituitary Adenoma: A Single Center Experience	Kim, J.	72	78
Human Folliculostellate Cell Line PDFS Facilitates the Formation of Tumor-like Structures in Human Pituitary Tumor Primary Cultures	Zhang, X.	Hot Topics	38
Hydrocephalus or Hypothalamic Involvement in Pediatric Patients with Craniopharyngioma or Cysts of Rathke's Pouch: Impact on Long-term Prognosis	Daubenbüchel, A.	4	44
Incidence of Acromegaly in a Large US Managed Care Population	Burton, T.	30	57
Influence of Dopamine Receptor Subtype 2 and Somatostatin Receptor Subtypes 2 and 5 Polymorphisms in Response to Treatment in Pituitary Adenomas	Bueno, C.	19	52
MSH3 Gene Missense Mutation as a Novel Molecular Pathogenesis of Dedifferentiated Chondrosarcoma in the Pituitary Region, a Sequencing-based Study	Gao, L.	45	65
Limitations of Current Approaches for Treatment of Acromegaly	Shanik, M.	31	58
Low Estrogen Receptor Alpha Expression is Associated with Male Gender and Poor Prognosis in Prolactin Tumors	Delgrange, E.	63	74
Macroprolactinemia Revisited	Glezer, A.	Invited Lecture	26
Management of Nelson's Syndrome and Invasive Corticotroph Tumors	Post, K.	Invited Lecture	26
Mechanisms for Prolactin Regulation of Reproduction	Binart, N.	Invited Lecture	33
Mifepristone	Fleseriu, M.	Invited Lecture	30
MiR-338-3p as a Tumor Suppressor Through Pttg Modulation in GH3 Cell Lines	Lee, Y.	32	58
Need for Improved Monitoring in Patients with Acromegaly	Silverstein, J.	33	59
Neuro-ophthalmologic Complication of a Nonfunctioning Adenoma During Pregnancy	Di Paolo, M.	69	77
No Excess Long-Term Mortality in the Finnish National Acromegaly Cohort – A Twenty-Year Follow-up Study	Ritvonen, E.	34	59
Non Suspected Thyrotropinoma: 15 Years Follow-up	Lopez, F.	50	67

ABSTRACT TITLE	Author	Poster #	PAGE
Oral Octreotide Therapy of Acromegaly	Popovic, V.	Invited Lecture	10
Pasireotide	Colao, A.	Invited lecture	29
Personality, Coping Strategies and Pain Appraisal in Patients with Tumors of the Sellar Region with and without Headache	Kreitschmann-Andermahr, I.	51	67
Pituitary Disorders in Pregnancy	Karaca, Z.	Invited Lecture	18
Pituitary Dysfunction in the Acute, Subacute and Chronic Phases of Traumatic Brain Injury (TBI)	Ojieh, G.	64	74
Pituitary Gigantism: Long-Term Follow-up of 13 Cases	Lecumberri, B.	35	60
Pituitary Tumor Stem Cells	Andoniadou, C.	Invited Lecture	34
Potential Factors Related to Treatment Changes in Acromegaly Patients: Analysis of a U.S. Prospective Registry	Carmichael, J.	36	60
Predictors of Central Diabetes Insipidus After Transsphenoidal Surgery	Crocker, E.	58	71
Pregnancies in Women Harboring Prolactinoma Treated with Cabergoline: Experience of a Single Center	Glezer, A.	65	75
Prevalence of Pituitary Adenomas at a Young University Hospital in Argentina	Sabate, M.	52	68
Prolactin Receptor Mutations	Thakker, R.	Invited Lecture	7
Prolonged Adjuvant Temozolomide Treatment in a Case of Aggressive ACTH-secreting Pituitary Adenoma	Iacovazzo, D.	15	50
Proteome Map of Adult Human Pituitary Glands	Mukherjee, K.	59	71
Puberty Mechanisms	Metzger, A.	Invited Lecture	33
Quality of Life in Patients with Acromegaly	Fujio, S.	37	61
Radiation-induced Sarcoma in Patients with Acromegaly	Erbas, T.	38	61
Rapid Remyelination Leads to Vision Recovery After Pituitary Tumor Resection	Paul, D.	Hot Topics	37
rhGH by Athletes: Is the Evidence Valid?	Holt, R.	Invited Lecture	15
Second Attempt of Cabergoline Withdrawal in Patients with Prolactinomas After a Failed First Attempt: Is it Worthwhile?	Vilar, L.	66	75
Secondary Hypothyroidism and an Enlarging Sellar Mass: An Unusual Case of Primary Pituitary Lymphoma	Desai, K.	46	65
Sellar Paraganglioma: A Case Report with 10 Year Follow-Up	Cox, S.	47	65
Single Center Surgical Experience in the Treatment of Prolactinomas	Donegan, D.	67	76
Successful Treatment with Somatostatin and Dopamine Analogues in A Patient with Nelson's Syndrome	Tkatch, J.	16	50
Surgeon Volume and Geography Impact Cost of Care for Pituitary Tumor Surgery	Lee, C.	60	72
Survival, Hypothalamic Obesity and Neuropsychological/Psychosocial Status After Childhood-onset Craniopharyngioma – Long-term Results in 261 Patients Recruited in HIT Endo	Sterkenburg, A.	5	45
Targeted Therapy for Aggressive Pituitary Tumors	Cooper, O.	Invited Lecture	27
Targeted Therapy for Aggressive Pituitary Tumours	Karavitaki, N.	Invited Lecture	27
The Establishment and Use of Database of Cushing's Disease	Feng, M.	17	51
The Prevalence of Multiple Endocrine Neoplasia-1 (MEN-1) in Acromegaly: Phenotype/Genotype Correlation	Torabi Sagvand, B.	20	52
The Thickened Pituitary Stalk with Papillary Carcinoma of the Thyroid: A Diagnostic Conundrum	Gordon, M.	61	73
The Value of Acute Octreotide Suppression Test in Predicting Short-term Efficacy of Somatostatin Analogues in Patients with Acromegaly	Shen, M.	39	62
Treatment of More than 5-Week Interval of Octreotide LAR in Patients with Acromegaly	Fukuda, I.	40	62
Treatment Patterns Among United States Acromegaly Patients in a Prospective Registry	Carmichael, J.	41	63
Use of Genomics in Elucidating Puberty	Pitteloud, N.	Invited Lecture	24
What Can We Learn by Measuring Circulating Growth Hormone Rhythms in Acromegaly?	Ribeiro-Oliveira Jr, A.	Invited Lecture	11
What's the Latest on Endocrine Effects of Traumatic Brain Injury?	Thompson, C.	Invited Lecture	24
Whole Exome Sequencing of FIPA Families without AIP Mutations	Sobreira, N.	73	79
X-Linked Acro-Gigantism (X-LAG) Syndrome: A New Form of Infant-onset Pituitary Gigantism	Stratakis, C.	Hot Topics	39

Abstract Index by Author

AUTHOR	Title	Poster #	PAGE
Geer, E.	A Multi-Center Study of Follow-up Intervals in Patients with Cushing's Disease	6	45
Gentilin, E.	ACTH-secreting Pituitary Adenomas: What Role for PRKCD?	70	77
Glezer, A.	Macroprolactinemia Revisited	Invited Lecture	26
Glezer, A.	Pregnancies in Women Harboring Prolactinoma Treated with Cabergoline: Experience of a Single Center	65	75
Gordon, M.	The Thickened Pituitary Stalk with Papillary Carcinoma of the Thyroid: A Diagnostic Conundrum	61	73
Hoffman, A.	Diencephalic Syndrome in Childhood Craniopharyngioma — Results of German Multicenter Studies on 485 Long-term Survivors of Childhood Craniopharyngioma	2	43
Hoffmann, A.	Childhood Craniopharyngioma	1	43
Hoffmann, A.	Eating Behavior and Weight Problems in Long-term Survivors of Childhood Craniopharyngioma – Results of the HIT ENDO Trial	3	44
Holt, R.	rhGH by Athletes: Is the Evidence Valid?	Invited Lecture	15
Hong, A.	Diagnostic Challenges in Pituitary Stalk Lesions: A Single Center Experience Over 10 Years	43	64
Iacovazzo, D.	Prolonged Adjuvant Temozolomide Treatment in a Case of Aggressive ACTH-secreting Pituitary Adenoma	15	50
Johnston, P.	Cushing's Disease and Co-existing Pheochromocytoma	10	47
Jørgensen, J.	GH-Induced Signaling in Human Muscle	Invited Lecture	14
Kamenický, P.	GH Regulation of Electrolyte Balance	Invited Lecture	14
Karaca, Z.	Pituitary Disorders in Pregnancy	Invited Lecture	18
Karavitaki, N.	Targeted Therapy for Aggressive Pituitary Tumours	Invited Lecture	27
Kasamo, Y.	Can Growth Hormone (GH) Replacement Therapy Improve Renal Function in Patients with GH Deficiency?	23	54
Kim, J.	Hormonal Outcome of Transsphenoidal Surgery in Patients with Nonfunctioning Pituitary Adenoma: A Single Center Experience	72	78
Kineman, R.	GH as a Metabolic Hormone	Invited Lecture	8
Kreitschmann-Andermahr, I.	Personality, Coping Strategies and Pain Appraisal in Patients with Tumors of the Sellar Region with and without Headache	51	67
Ku, C.	Comparison of Corticotropin Releasing Hormone and Desmopressin as Stimulators in Inferior Petrosal Sinus Sampling	9	47
Kuker, A.	Effect of Treatment with Pegvisomant on Bone Mineral Density and Bone Markers in Patients with Acromegaly	25	55
Labyer, L.	Case of Diabetes Insipidus (DI), Cerebral Salt Wasting (CSW) and Hypodipsic Hypernatremia	55	69
Lecumberri, B.	Pituitary Gigantism: Long-Term Follow-up of 13 Cases	35	60
Lee, C.	Surgeon Volume and Geography Impact Cost of Care for Pituitary Tumor Surgery	60	72
Lee, D.	A Silent Corticotroph Pituitary Adenoma Evolving into Clinical Cushing's Disease	7	46
Lee, Y.	MiR-338-3p as a Tumor Suppressor Through Pttg Modulation in GH3 Cell Lines	32	58
Lopez, F.	Non Suspected Thyrotropinoma: 15 Years Follow-up	50	67
Lu, L.	Experience of Bilateral Inferior Petrosal Sinus Sampling with DDAVP Stimulation Test in the Diagnosis of 275 Cases with the Cushing's Syndrome in a Single Center	14	49
Mangupli, R.	Combined Treatment with Octreotide LAR and Pegvisomant in Patients with Gigantism-Acromegaly	24	54
Mao, Z.	Differential Expression of MicroRNAs in GH-secreting Pituitary Adenomas with Responsiveness to Somatostatin Analogs	18	51
Martinez-Barbera, J.	Adamantinomatous Craniopharyngioma Contains Senescent Cells with Tumour-Inducing Potential	71	78
Metzger, A.	Puberty Mechanisms	Invited Lecture	33
Mukherjee, K.	Proteome Map of Adult Human Pituitary Glands	59	71
Ojieh, G.	Pituitary Dysfunction in the Acute, Subacute and Chronic Phases of Traumatic Brain Injury (TBI)	64	74
Oruk, G.	Gonadotroph Adenoma In Klinefelter's Syndrome	57	70
Paul, D.	Rapid Remyelination Leads to Vision Recovery After Pituitary Tumor Resection	Hot Topics	37

AUTHOR	Title	Poster #	PAGE
Petersenn, S.	Glucose and Lipid Levels After Lanreotide Autogel/Depot (LAN) 120mg in Treatment-naïve Patients with Acromegaly: Data from the PRIMARYS Study	29	57
Pitteloud, N.	Use of Genomics in Elucidating Puberty	Invited Lecture	24
Pivonello, R.	Efficacy and Safety of LCI699, A Potent 11β-hydroxylase Inhibitor, in Patients with Cushing's Disease: A 22-week, Multicenter, Open-label Study	Hot Topics	37
Popovic, V.	Oral Octreotide Therapy of Acromegaly	Invited Lecture	10
Post, K.	Management of Nelson's Syndrome and Invasive Corticotroph Tumors	Invited Lecture	26
Rau, H.	Chronic Hypopituitarism After Blast-related Concussion: Prevalence and Posttraumatic Symptomatology	56	70
Ribeiro-Oliveira Jr, A.	What Can We Learn by Measuring Circulating Growth Hormone Rhythms in Acromegaly?	Invited Lecture	11
Ritvonen, E.	No Excess Long-Term Mortality in the Finnish National Acromegaly Cohort – A Twenty-Year Follow-up Study	34	59
Sabate, M.	Prevalence of Pituitary Adenomas at a Young University Hospital in Argentina	52	68
Shafiq, I.	Disease Characteristics Associated with Cushing's Disease: A Multi-Center US Study	11	48
Shah, K.	Anterior Pituitary Dysfunction in Military Veterans with Mild Traumatic Brain Injury (mTBI): A Pilot Study	54	69
Shanik, M.	Limitations of Current Approaches for Treatment of Acromegaly	31	58
Shen, M.	The Value of Acute Octreotide Suppression Test in Predicting Short-term Efficacy of Somatostatin Analogues in Patients with Acromegaly	39	62
Silverstein, J.	Need for Improved Monitoring in Patients with Acromegaly	33	59
Singhal, V.	Gigantism: Detailed Clinical Characteristization of a Single Center Series	28	56
Sobreira, N.	Whole Exome Sequencing of FIPA Families without AIP Mutations	73	79
Sterkenburg, A.	Survival, Hypothalamic Obesity and Neuropsychological/Psychosocial Status After Childhood-onset Craniopharyngioma – Long-term Results in 261 Patients Recruited in HIT Endo	5	45
Stratakis, C.	X-Linked Acro-Gigantism (X-LAG) Syndrome: A New Form of Infant-onset Pituitary Gigantism	Hot Topics	39
Swearingen, B.	Determination of Remission after Surgery for Cushing's Disease	Invited Lecture	17
Syro, L.	Aggressive Pituitary Tumors or Localized Carcinomas	Invited Lecture	16
Thakker, R.	Prolactin Receptor Mutations	Invited Lecture	7
Thompson, C.	What's the Latest on Endocrine Effects of Traumatic Brain Injury?	Invited Lecture	24
Tkatch, J.	Successful Treatment with Somatostatin and Dopamine Analogues in A Patient with Nelson's Syndrome	16	50
Torabi Sagvand, B.	The Prevalence of Multiple Endocrine Neoplasia-1 (MEN-1) in Acromegaly: Phenotype/ Genotype Correlation	20	52
Trainer, P.	Evidence Based Guidelines in Acromegaly: Limitations and Utility	Invited Lecture	12
Tritos, N.	Cyclic Cushing's Syndrome	Invited Lecture	21
Valassi, E.	Evaluation of Bone Resistance Parameters in Active and Controlled Acromegaly and Matched Controls with Quantitative CT (QCT)	26	55
Vilar, L.	Efficacy and Safety of Retinoic Acid in Patients with Cushing's Disease: Results of a Prospective Study	12	48
Vilar, L.	Second Attempt of Cabergoline Withdrawal in Patients with Prolactinomas After a Failed First Attempt: Is it Worthwhile?	66	75
Wang, R.	Expert Consensus for Surgical Treatment of Pituitary Adenoma in China	48	66
Wu, Z.	Cabergoline Induces Autophagic Cell Death of Rat Pituitary Tumor Cells by Blocking Autophagic Flux	62	73
Yao, Y.	Endoscopic Biopsies of Lesions Associated with a Thickened Pituitary Stalk	44	64
Zhang, X.	Human Folliculostellate Cell Line PDFS Facilitates the Formation of Tumor-like Structures in Human Pituitary Tumor Primary Cultures	Hot Topics	38
Zhu, H.	A Retrospective Study on 51 Cases of Hypothalamic Syndrome and Metabolic Complications in Peking Union Medical College Hospital	42	63

Abstract Index By Poster Number

NOW APPROVED
IN THE UNITED STATES

Signifor® LAR

(pasireotide) for injectable suspension

20 mg, 40 mg, 60 mg

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

SIA-1107208

We hope to see you in 2017 in Orlando, Florida at the next Pituitary Congress.

Contact pituitarycongress@gmail.com for more information.