THE PITUITARY SOCIETY

presents the

18TH EIGHTEENTH INTERNATIONAL PITUITARY CONGRESS

JUNE 12 - 14, 2023

Chicago, Illinois

PROGRAM AND ABSTRACTS

THE DAVID L. KLEINBERG EARLY CAREER PITUITARY INVESTIGATOR PRIZE

Awards for the best manuscript, devoted to pituitary disease and or research, published by a young investigator in *Pituitary*.

Winners:

Cihan Atila

The effect of glucose dynamics on plasma copeptin levels upon glucagon, arginine, and macimorelin stimulation in healthy adults: Data from: Glucacop, Macicop, and CARGO study

Pituitary. 2022. PMID: 35723775

Liza Das

Long-term hepatic and cardiac health in patients diagnosed with Sheehan's syndrome

Pituitary. 2022 Dec;25(6):971-981. doi: 10.1007/s11102-022-01282-4. Epub 2022 Oct 15.

PMID: 36243797

MARCELLO BRONSTEIN MENTORSHIP IN PITUITARY MEDICINE AWARD

Award memorializes the legacy of a dedicated mentor to young endocrinologists worldwide who enjoyed the wise counsel and life lessons from an unforgettable role model who was larger than life itself.

Winner:

Mônica Gadelha

The Pituitary Society

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We hope to see you in 2025 in San Francisco, California at the next Pituitary Congress.

Contact info@pituitarysociety.org for more information.

We gratefully acknowledge educational grants and other support for the

18th International Pituitary Congress

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The CME Satellite Symposium

is supported by an educational grant from Novo Nordisk.

Welcome,

The Eighteenth International Pituitary Congress will present an exciting group of speakers expert in normal and disordered pituitary function. Our faculty includes distinguished clinicians and investigators, fellows in training, and basic scientists. As usual, we will present cutting edge in-depth topics that will permit our attendees to become familiar with the latest trends in pituitary endocrinology. The plenary format of the meeting is intended to facilitate maximum interaction and free exchange of ideas among participants and speakers.

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

We gratefully acknowledge the generous support and encouragement of our partners who are valued supporters of our Congress.

Welcome to two days of excellent science and companionship!

The Program Organizing Committee

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EIGHTEENTH INTERNATIONAL PITUITARY CONGRESS

MONDAY, JUNE 12th		
12.00 – 6.00 PM	**Registration**	
4.30 – 5.55 PM	**Early Career Development Forum**	*John Carmichael, Odelia Cooper, Adriana Ioachimescu*
OPENING PLENARIES ***Chairs: Maria Fleseriu & John Wass***		
6.00	**Using Mouse Models and Transcriptomics to Understand Stem Cell Behavior in Hypopituitarism**	*Lori Raetzman*
6.25	**AVP Deficiency: A New Look at a Classical Disease**	*Mirjam Christ-Crain*
NEW PITUITARY SOCIETY CONSENSUS GUIDELINES ***Chairs: Andrea Giustina & Lisa Nachtigall***		
6.50	**Consensus on Criteria for Acromegaly Diagnosis and Remission**	*Mônica Gadelha*
7.05	**The Pituitary Society 2021 Consensus Guideline Update on the Diagnosis and Management of Cushing's Disease**	*Ann McCormack*
7.20	**Diagnosis and Management of Prolactin-Secreting Pituitary Adenomas: Pituitary Society International Consensus Guidelines**	*Stephan Petersenn*
7.35	**Panel Discussion**	
8.00 - 10.00 PM	**Welcome Reception**	
TUESDAY, JUNE 13th		
7.00 AM	**Continental Breakfast**	
CUSHING'S ***Chairs: Beverly MK Biller & Rosario Pivonello***		
8.00	**Clinical Score for Screening of Cushing's Syndrome**	*Martin Reincke*
8.20	**Medical Therapy in Cushing's Syndrome**	*Greisa Vila*
8.40	**Patient Reported Outcomes in Cushing's Syndrome**	*Elena Valassi*
9.00	**Chronotherapy in Cushing's Therapy**	*John Newell-Price*
9.20	**Panel Discussion**	
9.40	**Coffee Break & Posters**	
TRANSLATIONAL SCIENCE ***Chairs: Richard Ross & Maria Chiara Zatelli***		
10.20	**Pituitary Immune Landscape**	*Yutaka Takahashi*
10.40	**The Third Hormone: Prolactin and Breast Cancer**	*Linda Schuler*
11.00	**Growth Hormone in the Aging Human Tissue Microenvironment**	*Vera Chesnokova*
11.20	**Growth Hormone: Role in Cancer**	*Jo Perry*
11.40	**Panel Discussion**	

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MEET-THE-PROFESSOR ***Each session will be repeated***		
12.00 NOON – 2.00 PM	**Aggressive Pituitary Adenomas**	*Mirela-Diana Ilie, Gérald Raverot*
	Central Hypothyroidism	*Biagio Cangiano, Luca Persani*
	Clinical Pearls/Discussion About Challenging Pituitary Cases	*Yona Greenman, Joanna Spencer-Segal*
	Glucocorticoid Withdrawal, Adrenal Insufficiency or Both?	*Irina Bancos, Rashi Sandooja*
	Multiple Endocrine Neoplasia and Pituitary Disease	*Leontine Bakker, Nienke Biermasz*
	Pituitary Diseases and Pregnancy	*Andrea Glezer, Anna Louise Stellfeld Monteiro*
	Postoperative Management of Pituitary Surgery	*Daniel Cuevas-Ramos, Elena Varlamov*
	Radiosurgery for Pituitary Adenomas	*Luigi Albano, Marco Losa*
	Updates on Pituitary Imaging	*Mark Gurnell, James MacFarlane*
	Value of Genetic Testing in Managing Pituitary Disease	*Fanny Chasseloup, Peter Kamenicky*
HOT TOPICS ***Chairs: Pouneh Fazeli & Marily Theodoropoulou***		
2.00	**Oxytocin in Hypopituitarism**	*Elizabeth Lawson*
2.15	**Mechanism Underlying Gigantism in Patients with X-LAG Syndrome**	*Albert Beckers*
2.30	**Opiates and Pituitary Function**	*Niki Karavitaki*
2.45	**Artificial Intelligence to Advance Surgical Therapy for Patients with Pituitary Adenoma**	*Hani Marcus*
3.00	**Coffee Break & Posters**	
CONCURRENT SESSIONS		
GROWTH HORMONE RESEARCH SOCIETY SYMPOSIUM ***Chair: Andrew Hoffman***		
3.45	**Growth Hormone Deficiency in Children**	*Adda Grimberg*
4.15	**Growth Hormone Deficiency in Adults**	*Andrew Hoffman*
4.45	**Growth Hormone in the Elderly**	*Pinchas Cohen*
INTERNATIONAL PITUITARY SURGEONS' SYMPOSIUM ***Chairs: Nelson Oyesiku & Kalmon Post***		
3.45	**Surgical Management of Craniopharyngiomas**	*Michael Buchfelder*
4.15	**Outcomes of Surgery in Acromegaly**	*Juan Fernandez-Miranda*
4.45	**Surgical Strategies in Cushing's Disease**	*Nelson Oyesiku*
5.15	**Poster Session**	
6.00 – 7.00 PM	**Congress Reception**	

 Continued from page 5

WEDNESDAY, JUNE 14th

7.00 AM	**Continental Breakfast**	
ACROMEGALY ***Chairs: Anna Maria Colao & Hidenori Fukuoka***		
8.00	**IGF-1 Variability and Other Potential Biomarkers of GH Activity**	*Philippe Chanson*
8.20	**Predicting SRL Responsiveness or Resistance**	*Diego Ferone*
8.40	**Experimental Medical Therapies**	*AJ van der Lely*
9.00	**Acromegaly and Bone**	*Melin Meliha Uygur*
9.20	**Acromegaly Registries**	*John Ayuk*
9.40	**Panel Discussion**	
10.00	**Coffee Break & Posters**	
ORAL PRESENTATIONS/YOUNG INVESTIGATOR AWARDS ***Chair: Jérôme Bertherat & Mercedes Piñeyro***		
10.30	**Epigenetic Control of Adamantinomatous Craniopharyngiomas**	*Clarissa Silva Martins*
10.35	**Accuracy of Biochemical Tests Differentiating Neoplastic from Non-neoplastic Hypercortisolism in Cushing's Syndrome: A Systematic Review and Meta-analysis**	*José Miguel Hinojosa-Amaya*
10.40	**Post-Operative Fluid Restriction Prevents Hyponatremia and Readmissions After Pituitary Surgery**	*Julia Chang*
10.45	**^{68}Ga-DOTATOC PET/CT in Localization of ACTH-Secreting Pituitary Tumors in the Patients with Cushing's Disease**	*Kyungwon Kim*
10.50	**Comparative Outcome of Surgical Versus Non-Surgical Treatment of Pituitary Apoplexy: Results from a Multi-Center International Observational Study of Pituitary Apoplexy**	*Adam Mamelak*
10.55	**Age-Dependent Risks and Benefits of Surgical Intervention for Pituitary Adenomas: Long-Term Surgical Outcomes at Our Institution**	*Yuki Shinya*
ROLE OF PATIENT SUPPORT GROUPS IN PITUITARY CLINICAL CARE AND RESEARCH ***Chairs: Eliza Geer & Laurence Katznelson***		
11.00	**Acromegaly Community**	*Jill Sisco*
11.15	**CSRF - Cushing's Support Research Foundation**	*Leslie Edwin*
11.30	**WAPO - World Alliance of Pituitary Organizations**	*Leslie Edwin*
CLOSING PLENARIES ***Chairs: Andrea Giustina & Shlomo Melmed***		
11.45	**Pituitary Adenoma Nomenclature: Consensus Statement**	*Ken Ho*
12.00 NOON	**Pituitary Tumors Centers of Excellence**	*Felipe Casanueva*
12.15 PM	**Presidential Address, Awards Presentation & Business Meeting**	*Kalmon Post*
12.50	**Congress Adjourns**	
1.15 - 2.25	**CME SATELLITE SYMPOSIUM** **Clinical Challenges of Adult Growth Hormone Deficiency (AGHD): A Case-Based Discussion to Improve Patient Outcomes**	

INVITED LECTURES
OPENING PLENARY SESSION

Chairs: Maria Fleseriu and John Wass

MF and JW have no relevant relationships to disclose.

Using Mouse Models and Transcriptomics to Understand Stem Cell Behavior in Hypopituitarism

Richard L. Gonigam, Karen E. Weis, Xiyu Ge, and Lori T. Raetzman

Department of Molecular and Integrative Physiology, University of Illinois Urbana-Champaign, Champaign, Illinois, USA

In humans and mice, loss of function mutations in growth hormone releasing hormone receptor (GHRHR) cause isolated growth hormone deficiency, a type of congenital hypopituitarism. The mutant GHRHR mouse model, $Ghrhr^{Lit/Lit}$ (LIT) exhibits loss of serum growth hormone, but also fewer somatotropes. However, how loss of growth hormone releasing hormone signaling affects expansion of stem and progenitor cells giving rise to growth hormone producing cells is unknown. LIT mice and wildtype littermates were examined for differences in proliferation and gene expression of pituitary lineage markers by quantitative real-time PCR and immunohistochemistry (IHC) at postnatal day 5 (p5) and 5 weeks. At p5, the LIT mouse shows a global decrease in pituitary proliferation measured by proliferation markers Ki67, and Phospho-Histone H3 (pH3). Surprisingly, SOX9 positive stem cells show no changes in proliferation in p5 LIT mice. The proliferative defect is seen in a pituitary cell expressing POU1F1 and GH, though 90% of the wildtype GH expressing cells are quiescent based on Ki67 IHC. Additionally, the other POU1F1 lineage cells do not show proliferation changes and are not decreased in number. Rather, we observe an increase in lactotrope cell population as well as mRNA for Tshb and Prl in p5 LIT mice. Treatment of neonatal cultured pituitary explants with GHRH promotes proliferation of POU1F1 expressing cells in a MAPK dependent manner, similar to what likely happens in vivo. In the 5 week LIT pituitary, the proliferative deficit in POU1F1 expressing cells observed neonatally persists, while the number and proliferative proportion of SOX9 cells, does not appear changed. Taken together, these findings indicate that hypothalamic GHRH targets proliferation of a POU1F1 positive cell, specified to the somatotrope lineage, to fine tune their numbers. Finally, we used available scRNA-seq data sets to determine gene expression differences in the proliferative somatotropes to uncover both unique markers and potential targets for therapy to selectively increase somatotrope number.

LR has no relevant relationships to disclose.

AVP Deficiency: A New Look at a Classical Disease

Mirjam Christ-Crain

University of Basel, Basel, Switzerland

AVP deficiency is a classical disease which was originally described as “diabetes insipidus” in the 18th century to differentiate it from “diabetes mellitus”. Only in the mid-20th century the distinct central and nephrogenic etiologies of diabetes insipidus were characterized.

Within the last years, many new developments in this classical disease took place. First, the differential diagnosis was challenged, which was for many decades done using the indirect water deprivation test as gold standard. New stimulation tests measuring copeptin as a surrogate marker for AVP are now available and simplify and improve the diagnostic procedure. Second, a group consisting of members of the main endocrine societies worldwide took the initiative to rename central diabetes insipidus to AVP deficiency due to persistent confusion with diabetes mellitus leading to fatal outcomes in some patients. Third, the recognition of psychological problems in many patients with AVP deficiency led to the hypothesis that some of these patients might also have oxytocin deficiency.

This talk will discuss these different topics and highlight the most important developments within the last year.

MC-C has no relevant relationships to disclose.

NEW PITUITARY SOCIETY CONSENSUS GUIDELINES

Chairs: Andrea Giustina and Lisa Nachtigall

AG receives consulting fees from Ipsen, Pfizer, and Recordati; LN receives grant funds from Recordati, consulting fees from Corcept, and grant funds and consulting fees from Amryt.

Consensus on Criteria for Acromegaly Diagnosis and Remission

Mônica Gadelha

Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

GH and IGF-I measurements are commonly used as biochemical markers of disease activity for diagnosis and follow-up management of acromegaly. Criteria for diagnosis and therapeutic goals were defined at the first Acromegaly Consensus Conference held in 1999 in Cortina, Italy, revised in 2010 at the 7th Acromegaly Consensus Conference, and further adjusted in 2014 in guidelines from the Endocrine Society. Following on studies underscoring the challenges of uniformly applying results of GH and IGF-I assays in the clinic, the 14th Acromegaly Consensus Conference held in 2022 in Stresa, Italy, once again revisited the question of how to define biochemical criteria for acromegaly diagnosis and evaluation of therapeutic efficacy. Fifty-six acromegaly experts from 16 countries reviewed and discussed current literature on 22 discrete topics in 7 workshops focused on biochemical assays; criteria for diagnosis and the role of imaging, pathology, and clinical assessments; consequences of diagnostic delay; criteria for remission and recommendations for follow up; and the value of assessment and monitoring in defining disease progression, selecting appropriate treatments, and maximizing patient outcomes. Consensus recommendations highlight new understandings of GH and IGF-I activity in patients with acromegaly and the importance of expert management for this rare disease.

MG receives consulting fees and honorarium from Crinetics, Ipsen, Recordati and NovoNordisk.

The Pituitary Society 2021 Consensus Guideline Update on the Diagnosis and Management of Cushing's Disease

Ann McCormack

St Vincent's Hospital Sydney and Garvan Institute of Medical Research, Australia

In October 2020, the Pituitary Society hosted a 2-day virtual workshop including experts from 13 countries to systematically discuss advances in the diagnosis and management of Cushing's disease. Notable updates from previous guidelines, last published in 20151, will be presented. These include non-invasive alternatives to inferior petrosal sinus sampling in distinguishing pituitary versus ectopic causes of hypercortisolism, advances in imaging and genetic insights as well as the role of newly approved medical therapies particularly osilodrostat. The consensus paper also highlighted key future research topics based on knowledge gaps in the field that will be discussed.

[1] Nieman LK et al. Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2015:100:2807-31

AM has no relevant relationships to disclose.

Diagnosis and Management of Prolactin-Secreting Pituitary Adenomas: Pituitary Society International Consensus Guidelines

Stephan Petersenn (on behalf of participants of the consensus workshop)

ENDOC Center for Endocrine Tumors, Hamburg, Germany, and University of Duisburg-Essen, Essen, Germany

In 2006, the Pituitary Society published its first guidelines on the diagnosis and management of prolactinomas (1), which were updated in 2011 jointly by the Pituitary Society and the Endocrine Society (2). As considerable progress has been made in pituitary science during the last decade, an internationally agreed update appeared necessary. Therefore, in 2022, the Pituitary Society hosted a virtual consensus workshop on the management of prolactinoma, including 36 experts representing 13 countries with different healthcare systems. Important topics were identified, and speakers selected according to their expertise summarized key data and critically reviewed the literature. Workshop participants were divided into breakout groups for extended discussions, and then reported their conclusions and comments to the entire group. Consensus recommendations were recorded based on majority opinion. The draft manuscript was circulated to all authors in 3 rounds prior to their final approval, and is currently under review (3).

Importantly, it presents the latest evidence on treatment of prolactinoma, including dopamine agonist efficacy, side effects, and options for withdrawal, as well as updated indications for surgery. Furthermore, management of prolactinoma in special situations is discussed, including cystic lesions, mixed growth hormone and prolactin-secreting adenomas, and aggressive prolactinomas, considerations for pregnancy and fertility, as well as management of prolactinomas in children and adolescents, patients with underlying psychiatric disorders, menopausal women, transgender individuals, and patients with chronic kidney disease.

Hopefully, the updated consensus will further improve the diagnosis and management of our patients with prolactinomas.

References:

1. Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, Brue T, Cappabianca P, Colao A, Fahlbusch R, Fideleff H, Hadani M, Kelly P, Kleinberg D, Laws E, Marek J, Scanlon M, Sobrinho LG, Wass JA, Giustina A. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf). 2006;65:265-273.
2. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA, Endocrine S. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:273-288.
3. Petersenn S, Fleseriu M, Casanueva FF, Giustina A, Biermasz N, Biller B, Bronstein M, Chanson P, Fukuoka H, Gadelha M, Greenman Y, Gurnell M, Ho K, Honegger J, Ioachimescu A, Kaiser U, Karavitaki N, Katznelson L, Lodish M, Maiter D, Marcus HJ, McCormack A, Molitch M, Muir CA, Neggers S, Pereira AM, Pivonello R, Post K, Raverot G, Salvatori R, Samson S, Shimon I, Spencer-Segal J, Vila G, Wass J, Melmed S. Diagnosis and Management of Prolactin-Secreting Pituitary Adenomas: Pituitary Society International Consensus Guidelines. 2023; under review.

SP has no relevant relationships to disclose.

CUSHING'S

Chairs: Beverly MK Biller and Rosario Pivonello

BMKB receives consulting honorarium from Recordati, Sparrow and Xeris; RP receives consulting fees from Recordati and Corcept and research fees from Strongbridge.

Clinical Score for Screening of Cushing's Syndrome

Martin Reincke

MR has no relevant relationships to disclose.

Medical Therapy in Cushing's Syndrome

Greisa Vila

Dept. of Endocrinology and Metabolism, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

Medical therapy in Cushing's has evolved considerably during the last decades. The availability of several drugs with different targets and potencies allows choosing the right therapy for each patient based on his comorbidities, disease source, and grade of hypercortisolism. This talk will cover an overview of the drug classes used in the treatment of hypercortisolism, and clinical situations necessitating a medical therapy.

Current therapies target somatostatin and dopamine receptors in pituitary corticotrophs, adrenal steroidogenesis and glucocorticoid receptors. Among all these drugs, adrenal steroidogenesis inhibitors are potent inhibitors of hypercortisolism and very effective in severe disease. This class includes ketoconazole, metyrapone, mitotane, etomidate, osilodrostat and the recently US-approved levoketoconazole. Pituitary-targeting therapies like somatostatin receptor ligands and dopamine receptor agonists (the later not approved for this indication) are best used in mild central disease and are shown to reduce tumor-mass. The glucocorticoid receptor blocker mifepristone is approved for hypercortisolism accompanied by uncontrolled hyperglycemia.

In the clinical praxis, medical therapy is not only used in persisting chronic disease after surgery, or when surgery is not feasible, but also in selective cases prior to surgery. While the number of randomized clinical studies on the efficacy of Cushing's therapeuticals is increasing, data on the short preoperative use of medical therapy come mainly from retrospective cohort studies. Nevertheless, the high prevalence of life-threatening events and the high mortality observed in the initial months after disease diagnosis necessitate a rapid reduction of hypercortisolism, which in turn helps stabilizing clinical comorbidities prior to surgery.

In the daily praxis, the type of disease, patient characteristics, as well as drug-specific adverse effects, should be taken into account when choosing the most appropriate Cushing's therapy for each single patient. Internationally, this choice might be limited by country-specific drug availability and costs.

GV receives consulting fees and honoraria from Recordati.

Patient Reported Outcomes in Cushing's Syndrome

Elena Valassi

Hospital de la Santa Creu, Sant Pau, Barcelona, Spain

Patient-reported outcome measures (PROMs), including evaluation of Quality of Life (QoL), should complement biochemical and radiological workup of patients with Cushing's syndrome (CS). Health perception is impaired in patients with active disease and often remains poor even after endocrine "cure" is reached, partly due to the long-term persistence of physical morbidity, cognitive dysfunctions, affective disorders and a negative illness perception. This may severely affect patient's social, professional and family domains, and also cause a significant socioeconomic burden. Because adaptation to the new psychophysical limitations is associated with better health perception and Qol, PROMs evaluation should be carried out throughout all the phases of the disease in order to identify the unmet needs and specifically address them within a multidisciplinary approach. This is particularly important in light of a frequent dissociation between patients' and physicians' health perception, with the latter often underrecognizing and undertreating the most bothersome symptoms. Individualized educational programs and focus group should be promoted, also through the new technologies, to empower patients, increasing self-management, self-confidence and acceptance process to the new situation. To join patient associations may be useful to overcome feelings of isolation. Raising awareness among health professionals from a range of disciplines on signs and symptoms of this rare disease also appears fundamental to shorten delay to diagnosis, which is strictly associated with the sustained burden of hypercortisolism.

EV has no relevant relationships to disclose.

Chronotherapy in Cushing's Therapy

John Newell-Price

University of Sheffield, UK

Metabolism is governed by internal cellular clocks that synchronize with the daily circadian rhythm through external cues that are entrained on a daily basis. The endocrine system plays a major role in mediating signals from central to peripheral clocks. Dysregulation of circadian rhythms, including those for cortisol, are associated with worse cardiovascular and metabolic outcomes.

Cushing's syndrome is an exemplar of dysregulated circadian cortisol secretion, with associated morbidity and mortality. To date, most treatment outcomes have focused on overall control of cortisol burden as reflected by control of 24-hour urinary free cortisol (UFC). Whilst UFC represents one level of control, more recent data suggest that additional control of the cortisol circadian rhythm is associated with better outcomes. Attention by clinicians, industry and licensing authorities to this 'chronotherapy', and not relying solely on UFC as a measure of control for Cushing's syndrome, is likely to improve outcomes for patients.

JN-P is on the Scientific Advisory Boards for HRA Pharma and Recordati; fees paid to the University of Sheffield.

TRANSLATIONAL SCIENCE

Chairs: Richard Ross and Maria Chiara Zatelli

RR receives consulting fees from Neurocrine; MCZ has no relevant relationships to disclose.

Pituitary Immune Landscape

Yutaka Takahashi

Department of Diabetes and Endocrinology, Nara Medical University, Japan

A representative autoimmune condition in the pituitary, hypophysitis is classified according to the anatomic location of pituitary involvement and the cause (primary or secondary forms). The primary forms are characterized by an idiopathic autoimmune inflammatory process confined to the pituitary gland, while the secondary forms are triggered by a definite etiology. Recently, as a secondary form of hypophysitis, an immune-mediated paraneoplastic syndrome defined as paraneoplastic autoimmune hypophysitis has emerged.

This novel clinical entity, paraneoplastic autoimmune hypophysitis consists of several conditions such as anti-PIT-1 hypophysitis and a part of isolated ACTH deficiency and immune checkpoint inhibitor-related hypophysitis with common underlying mechanisms, in which an ectopic pituitary antigen expression in the complicated tumor evoked autoimmunity against pituitary-specific antigens, resulting in hypophysitis and leading to the impairment of specific anterior pituitary cells by cytotoxic T cells. The concept of paraneoplastic autoimmune hypophysitis give us a new aspect and these conditions can explain at least in part, the underlying mechanisms of acquired specific pituitary hormone deficiencies. In addition, it is important to apply a discipline of onco-immuno-endocrinology to understand the pathophysiology comprehensively.

YT has no relevant relationships to disclose.

The Third Hormone: Prolactin and Breast Cancer

Linda A. Schuler

Dept. of Comparative Biosciences, University of Wisconsin-Madison, Madison, Wisconsin, USA

Prolactin interacts with estrogen and progesterone to orchestrate mammary development during pregnancy and lactation. Its central roles in physiological mammary epithelial growth and differentiation suggest that it acts in breast cancer, but it has been challenging to identify its contributions, which is essential for incorporation into prevention and treatment approaches. Large prospective epidemiologic studies have linked higher prolactin exposure to increased risk, particularly for ER+ breast cancer in postmenopausal women. However, its actions and clinical consequences in established tumors remain controversial. Our NRL-PRL murine model, which elevates local mammary prolactin concentrations, has enabled study of the actions of prolactin and interactions with ovarian steroids outside of pregnancy. Nulliparous NRL-PRL females spontaneously develop histologically diverse, metastatic ER+ carcinomas with long latencies, mimicking the epidemiologic link between prolactin exposure and aggressive ER+ cancer. To understand how prolactin influences mammary epithelial subpopulations, we examined effects of prolactin in concert with defined exposure to ovarian steroids following postpubertal ovariectomy. Local prolactin modulated transcriptional programs to expand luminal epithelial progenitors independently from estrogen/ progesterone, and cooperated with ovarian steroids to increase stem cell activity. This increase in potential tumor cells of origin in conjunction with prolactin-induced epithelial proliferation observed in this and other models, and potential prolactin actions on other cell types predicted by non-tumor models, begin to elucidate the mechanisms by which prolactin may increase the risk of breast cancer. In clinical breast cancers, prolactin receptors are expressed in many tumors across all different subtypes, and epidemiologic analyses and experimental studies indicate that prolactin can elicit both pro-differentiation and pro-aggression outcomes. To illuminate tumor extrinsic factors that may influence the role(s) of prolactin in disease progression, we examined the effect of characteristics of the extracellular matrix on prolactin-initiated downstream signaling cascades and tumor behavior. Our studies showed that increased matrix density/ stiffness of the tumor microenvironment shifts the repertoire of prolactin-induced signaling pathways away from the pro-differentiation JAK2-STAT5 signaling cascade, toward pathways associated with tumor aggression (FAK/SFK, ERK1/2, AKT) and increased metastasis in vivo. Together, these studies and other current approaches are revealing the biology behind the seemingly conflicting studies of prolactin actions across diverse breast cancers.

LS has no relevant relationships to disclose.

Growth Hormone in the Aging Human-Tissue Microenvironment

Vera Chesnokova[1], Svetlana Zonis[1], Tugce Apaydin[1], Robert Barrett[2], Shlomo Melmed[1]

[1]Department of Medicine and [2]Board of Governors Regenerative Medicine Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA

The aging tissue microenvironment undergoes progressive changes enabling age-related pathologies. Senescence is an important defense mechanism against cancer, as it prevents proliferation of cells with damaged DNA, and senescent cells also increase with age. Furthermore, the senescent-associated secretome (SASP) regulates neighboring cell proliferation, inflammation, angiogenesis, and, depending on tissue type, creating a milieu favoring neoplasia. We previously showed that growth hormone (GH) is induced in response to DNA damage and suppresses DNA repair. Here we present evidence that GH is induced in different types of cell senescence. We are engaged in studying SASP-derived GH actions on the tissue microenvironment and show that GH is a functional SASP component and accumulates with age in human colon tissue. When human colonocytes were cultured on a Colon- Intestine Chip (Emulate) in the presence of human colon fibroblasts secreting GH , they exhibited p53/p21 pathway suppression with induced proliferation and increased DNA damage. In the colon tissue of mice with GH-secreting xenografts and high circulating GH, p53 was also suppressed in vivo, while unrepaired DNA damage accumulated. In contrast, in mice with GH signaling deficiency ($GHR^{-/-}$) we observed induced p53 with less DNA damage. Direct paracrine effects of GH were then examined in intact human 3D intestinal organoids co-cultured with organoids infected with lentivirus expressing either hGH (lentiGH) or vector (lentiV). Using whole-exome sequencing, we found that local paracrine GH emanating from lentiGH organoids induces chromosomal instability in intact organoid cells, with somatic mutations including deletions, breakends and duplications, as compared to organoids co-cultured with lentiV-expressing control organoids. We demonstrate mechanisms for SASP-induced GH action on chromosomal instability which include induction of phosphatase WIP1 which de-phosphorylates DNA repair proteins including pATM, pATR, and pBRCA2, leading to suppressed DNA repair and subsequent DNA damage accumulation. These changes favor GH-mediated cell transformation evidenced by suppressed E-cadherin and increased Twist2, markers of EMT. Indeed, KEGG pathway analysis of intact organoids subjected to paracrine GH exposure identified changes in focal adhesion pathways, consistent with increased migration, invasion, and anchorage-independent growth of normal human colon cells (hNCC) exposed to GH. These results identify local paracrine GH secreted from senescent cells as an important determinant of the local tissue microenvironment promoting age-associated changes consistent with chromosomal instability and a pro-neoplastic milieu.

VC has no relevant relationships to disclose.

Growth Hormone: Role in Cancer

Jo K. Perry

Liggins Institute, University of Auckland, Auckland, New Zealand

Decades of published research supports a role for growth hormone (GH) in cancer. Clinically, increased GH levels have been identified in the sera of cancer patients and in various tumour types. GH and GH receptor expression levels correlate with poorer clinical and histopathological parameters in certain cancers. Accordingly, there has been increased interest in targeting the GH receptor in oncology, with GH antagonists exhibiting efficacy in xenograft studies as single agents and in combination with anticancer therapy or radiation. This presentation will review evidence supporting a role for GH in cancer with a focus on recent progress in the field. Challenges associated with using GH receptor antagonists in preclinical models will be discussed as well as considerations for translation.

JP has no relevant relationships to disclose.

MEET THE PROFESSOR
Aggressive Pituitary Adenomas

Mirela Ilie, Gérald Raverot

Hospices Civils of Lyon-Lyon1 University, Lyon, France

Although usually benign, anterior pituitary adenomas occasionally exhibit aggressive behavior, with rapid growth, resistance to conventional treatments, and multiple recurrences. In very rare cases, they metastasize, being termed pituitary carcinomas. Future aggressive behavior remains difficult to predict. Nevertheless, a clinicopathological classification identified a group of tumors, invasive and proliferative (2b), representing less than 10% of surgical series, as having greater risk of recurrence or resistance to conventional treatment. In addition, an initial Ki67 index ≥10% is associated with worse outcome and appears as a promising early marker of future metastasis. Generally, the initial therapeutic approach for aggressive pituitary adenomas is to repeat surgery or radiotherapy in expert centers. Standard medical treatments have usually no effect on tumor progression, but they can be maintained on a long-term basis to control, at least partly, hypersecretion. After the failure of standard treatments, temozolomide is for the moment the sole formally recommended treatment. However, it is effective in only one-third of patients. Emerging therapies, such as immunotherapy and angiogenesis-targeted therapy show a certain efficacy, with immunotherapy appearing as a good second-line therapy for pituitary carcinomas. In the case metastases are present, local treatment should be taken into consideration, independent of whether systemic treatment is used.

In this "Meet-the-Professor" session, we will use clinical cases to illustrate this complex topic, including definition, epidemiology, predictive markers of future aggressive behavior, and treatment, covering both efficacy and predictive factors of response. The aim is to provide the attendees with key clinical aspects that can be readily implemented in the management of these rare but challenging tumors.

M-DI and GR have no relevant relationships to disclose.

This presentation will include discussion of products 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.

Central Hypothyroidism

Luca Persani, Biagio Cangiano

University of Milan and IRCCS Istituto Auxologico Italiano, Milan, Italy

Central Hypothyrodism (CeH) is a hypothyroid state caused by an insufficient stimulation by thyrotropin (TSH) of an otherwise normal thyroid gland. This is a rare but still too frequently unrecognized clinical condition. This is mainly due to the high prevalence of primary hypothyroidism and the diffuse use of the "reflex TSH strategy" to screen thyroid function. CeH is indeed the principal false negative result of such screening strategy because low FT4 with low/normal TSH levels are the biochemical hallmark of CeH. CeH is still most frequently diagnosed as consequence of the biochemical assessments in patients with hypothalamic/pituitary lesions but several advancements, including the publication of the ETA expert guidelines for CeH diagnosis and management, have been made in recent years thus increasing the clinical awareness on this condition. Indeed, CeH can be the consequence of various disorders affecting either the pituitary gland or the hypothalamus. Recent data enlarged the list of candidate genes for heritable CeH and a genetic origin may be the underlying cause for CeH discovered in pediatric or even adult patients without apparent pituitary lesions. This confirms the hypothesis that the frequency of CeH may be underestimated. Adequate thyroid hormone replacement leads to the suppression of residual TSH secretion. Thus, CeH often represents a clinical challenge because physicians cannot rely on the use of TSH as index for therapy monitoring. Nevertheless, in contrast with general assumption, the finding of normal TSH levels may indicate thyroxine under-replacement in CeH patients. The clinical management of CeH is further complicated by the combination with multiple pituitary deficiencies, as the introduction of sex steroids or GH replacements may uncover latent forms of CeH or increase the thyroxine requirements.

BG and LP have no relevant relationships to disclose.

Clinical Pearls/Discussion About Challenging Pituitary Cases

Yona Greenman[1], Joanna Spencer-Segal[2]

[1]Tel Aviv-Sourasky Medical Center, Institute of Endocrinology and Metabolism, Tel Aviv, Israel; [2]Department of Internal Medicine and Michigan Neuroscience Institute, University of Michigan, Ann Arbor, Michigan, USA

This session will include discussion of clinical pearls in difficult cases from the practices of two expert pituitary endocrinologists. Topics will include decisions surrounding surgical or medical management of functional tumors, and tailoring treatment choices to patient preferences and medical comorbidities.

YG has no relevant relationships to disclose; JS-S receives research funding from Recordati.

Glucocorticoid Withdrawal, Adrenal Insufficiency, or Both?

Irina Bancos, Rashi Sandooja

Division of Endocrinology, Mayo Clinic, Rochester, Minnesota, USA

Glucocorticoid withdrawal syndrome (GWS) is a constellation of symptoms that occurs after successful curative surgery for either ACTH-dependent or ACTH-independent Cushing Syndrome (CS). GWS occurs despite a supra-physiological glucocorticoid replacement initiated for post-operative adrenal insufficiency.

Symptoms of GWS vary in severity, and include symptoms of myalgia, arthralgia, fatigue, hypersomnolence, nausea, mood changes, and headaches. Some symptoms of GWS overlap with those of adrenal insufficiency, and may improve with temporary increase in the glucocorticoid dose. Management of GWS varies, usually individualized to patient's circumstances, and informed by the individual endocrinologist's experience.

In this case-based discussion, we aim to 1) describe GWS severity and trajectory, 2) identify factors associated with GWS, 3) discuss management strategies of GWS.

IB and RS have no relevant relationships to disclose.

Multiple Endocrine Neoplasia and Pituitary Disease

Nienke R Biermasz, Leontine EH Bakker

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

Multiple endocrine neoplasia type 1 (MEN1) is a genetic disease that predisposes carriers to development of various endocrine neoplasms, among which pituitary adenomas. The prevalence of clinically relevant pituitary adenomas in this condition is considered to be 20-25%. With periodical screening also incidentaloma will be detected.

In this Meet-the-Professor session we will review available review on prevalence, clinical characteristics, surveillance and management strategies of MEN1-related pituitary adenomas, both non-functioning and functioning. In general, the management of pituitary adenoma is not different from non-MEN 1 related cases. However, there are some issues to take into account.

Based on clinical cases examples we stress challenges in MEN1-related pituitary disease:

- Pediatric pituitary adenoma
- When to consider MEN in pituitary adenomas?
- Surveillance protocols and lifetime intervention planning
- Pituitary adenoma and MEN related comorbidity
- The differential diagnosis of ectopic disease
- Refractory tumors, recurrences and aggressive tumors in MEN

NB and LB have no relevant relationships to disclose.

Pituitary Diseases and Pregnancy

Anna Louise Stellfeld Monteiro, Andrea Glezer

Neuroendocrine Unit, Division of Endocrinology and Metabolism, Hospital das Clinicas, University of Sao Paulo Medical School, Sao Paulo, Brazil

During pregnancy, pituitary gland increases in size and modifies its function, mainly by placental hormonal secretion. Gonadotrophins are suppressed, TSH can be suppressed during the 1st trimester, hyperprolactinemia and hypercortisolism occur specially after the 2nd trimester and placental GH is the major responsible for IGF-1 secretion. The knowledge of these physiological modifications during gestation is important to manage pituitary diseases before, during and after pregnancy.

Due to advances in medical and surgical treatments of pituitary adenomas, pregnancy has become a reality for women harboring such tumors. Regarding prolactinomas, hyperprolactinemia should be treated to revert hypogonadism, allowing pregnancy, usually by dopamine agonists (DA). Although high estrogen levels secreted by placenta increases normal pituitary gland and prolactinoma sizes, micro and intrasellar macroprolactinomas rarely present tumor growth with clinical symptoms. Therefore, DA are usually withdrawn after pregnancy confirmation. In acromegaly, high estrogen levels can reduce hepatic IGF-1 secretion. Usually there is tumor stability and hormonal control during pregnancy, allowing SRL withdrawn after pregnancy confirmation. Cushing disease is uncommonly diagnosed during pregnancy, and it is a diagnostic challenge. Severe hypercortisolism can impact in maternal and fetal outcomes during pregnancy and should be treated. Clinically non-functioning pituitary tumors usually affect patients aged 50 and older and rarely women childbearing age. Although these tumors do not increase during pregnancy, normal pituitary gland increases, which could lead to symptoms related to mass effect.

Ovulation induction and proper hormonal replacement, adjusted for each trimester, have enabled safe pregnancies for patients with hypopituitarism. For central hypothyroidism, increase in T4 doses is recommend, considering total T4 levels. GH replacement is important to improve ovulation quality and can be withdrawn after the 1st trimester due to GH secretion by placenta. Glucocorticoid replacement dosages should be evaluated, especially in the 3rd trimester, and doses must be increased during delivery. DDAVP doses can be increased after the 2nd trimester in patients with ADH deficiency and should be administered in patients who present ADH deficiency only during pregnancy (gestational DI).

Also, there are pituitary diseases related to pregnancy as Sheehan´s Syndrome (ShS) and lymphocytic hypophysitis. ShS is characterized by hypopitutarism secondary to pituitary necrosis due to hypovolemic shock related to uterine bleeding during/after delivery. Although rare nowadays due to improved perinatal care, this condition should be kept in mind in puerperal patients, especially for those with severe post-partum bleeding and agalactia with no history of hypopituitarism and/or pituitary tumor. Lymphocytic hypophysitis is an autoimmune disease characterized by predominant lymphocytic infiltration, and it may lead to pituitary tissue destruction and fibrotic reaction, with subsequent hypopituitarism. It is associated with pregnancy in more than 20% of cases and clinical picture includes headaches, visual impairment, anterior hypopituitarism (ACTH deficiency preferentially is a clue for diagnosis) and ADH deficiency. The diagnosis is usually made on a clinical suspicion basis as definitive diagnosis depends on anatomopathological evaluation.

ALSM and AG have no relevant relationships to disclose.

This presentation will include discussion of products 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.

Postoperative Management of Pituitary Surgery

Daniel Cuevas-Ramos[1], Elena Varlamov[2]

[1]Neuroendocrinology Clinic, Chief, Department of Endocrinology and Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico; [2]Departments of Medicine (Endocrinology) and Neurological Surgery, and Pituitary Center, Oregon Health & Science University, Portland, Oregon, USA

Background

Pituitary tumors are benign neoplasms that could be clinically functional or non-functional. Surgery the first line therapy for large tumors, acromegaly, and Cushing's disease (CD). Prolactinomas usually are treated with dopamine agonists (DA) but some have surgical indication.

Aims: to describe postoperative management of pituitary adenomas.

Results: transsphenoidal surgery (TSS) is the primary treatment for non-functioning pituitary adenomas if there is mass effect (anterior hypopituitarism, visual loss due to optic chiasm/nerve compression, or apoplexy), clinically significant growth, or unremitting headaches. Evaluation for hormonal deficiencies or overproduction is recommended. In the early postoperative period, diabetes insipidus (DI)

occurs in 18-30% of patients but usually resolves in 90% after several weeks. Close evaluation for DI (hypernatremia), and syndrome of inappropriate antidiuretic hormone secretion (hyponatremia) is necessary to prevent mortality. Postoperative hypotension may suggest new adrenal insufficiency (AI). The thyroid and gonadal axis should be evaluated. Cerebrospinal fluid leak, hemorrhage, and meningitis each occur in up to 1% of operated patients. Serum measures of growth hormone (GH) after TSS for acromegaly are of limited value because GH has a short half-life and pulsatile secretion. Also, cutoff levels to define remission are unclear. Age- and gender-adjusted level of IGF-1 is more reliable marker of remission. IGF-1 levels take longer to normalize, so, first evaluation should be delayed to 6-12 weeks postoperatively. Perioperative management of CD includes measurement of cortisol/ACTH early after surgery to assess for remission, appropriate glucocorticoid coverage and management and prevention of comorbidities. Patients with resistant and aggressive prolactinomas or DA intolerance may require surgery; remission is assessed by postoperative prolactin measurement and imaging.

Conclusions: Postoperative evaluation of hormone deficiencies is important to prompt therapy and avoid complications. Timeline of assessment of biochemical remission in functioning pituitary adenomas varies based on tumor type.

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DC-R has no relevant relationships to disclose; EV receives research support (to her institution) from Recordati and Lumiio/Pfizer.

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

Radiosurgery for Pituitary Adenomas

Marco Losa, Luigi Albano, Raffaella Barzaghi, Pietro Mortini

Dept. of Neurosurgery, Istituto Scientifico San Raffaele, University Vita-Salute, Milan, Italy

Radiotherapy has, historically, played a central role in the management of patients with pituitary adenomas. In recent years, we have experienced a substantial improvement in the methodology of radiation therapy. In particular, the introduction of highly targeted radiotherapy, such as Gamma Knife radiosurgery GKRS), has further increased the therapeutic options available in the management of pituitary tumors. Nowadays, GKRS, the most used stereotactic radiosurgery technique worldwide, is used in cases of residual or recurrent tumors after surgery or as primary treatment when surgery is contraindicated. The goals of GKRS are long-term tumor control and, for secreting pituitary adenomas, endocrine remission.

The results of several studies confirm that GKRS has a good efficacy to reverse hormone hypersecretion and control tumor growth in most cases of pituitary adenomas. The safety profile of GKRS has been well demonstrated. Severe adverse events are rare, while the risk of hypopituitarism in cases with favorable morphological features may be very low.

GKRS should be considered in the setting of adjuvant treatment of pituitary adenomas that have not been controlled by pituitary surgery.

ML has no relevant relationships to disclose; LA receives other financial benefit from Leksell Gamma Knife Society.

Updates on Pituitary Imaging

James MacFarlane, Mark Gurnell

Cambridge Endocrine Molecular Imaging Group, Wellcome–MRC Institute of Metabolic Science & Department of Medicine, University of Cambridge & Addenbrooke's Hospital, Cambridge, UK

Anatomical imaging techniques [e.g. magnetic resonance imaging (MRI) and computed tomography (CT)] are indispensable cornerstones in the management of sellar and parasellar disorders. For most patients with pituitary tumors, high quality standard MR sequences [T1-weighted Spin Echo (T1SE) ± gadolinium and T2 fast/turbo SE (T2FSE/TSE)] performed at 3 Tesla (3T) allow clear visualization of the tumor and important surrounding neurovascular structures. However, even when performed in Pituitary Tumors Centers of Excellence (PTCOE), an important subgroup of pituitary adenomas are not readily visualised – both *de novo* cases (e.g. corticotroph, somatotroph, lactotroph or thyrotroph microadenomas), and following primary or secondary surgery (e.g. in patients with persistent Cushing disease or acromegaly). In other patients, discrimination between residual tumor and post-treatment tissue remodelling is particularly challenging and may preclude further attempts at definitive treatment (e.g. surgery or stereotactic radiosurgery).

Another important limitation of conventional sella imaging is the difficulty in reliably distinguishing between tumors which are likely to grow/recur versus those which will follow a more indolent course. Although initial tumor size and extent of parasellar invasion are important indicators of a propensity to recur and to invade surrounding structures, not all large tumors demonstrate such behavior and vice versa.

In this session, we will use a series of illustrative cases to highlight recent developments in pituitary imaging, with reference to both anatomical and functional [i.e. molecular, e.g. positron emission tomography (PET)] techniques. Specifically, we will examine how:

- the deployment of additional (non-standard) MR sequences can facilitate the detection of microadenomas which are not otherwise readily visualized
- augmented analyses of standard pituitary MR sequences (including radiomics) may provide novel information regarding future tumor behavior
- the introduction of increased field strength MRI (e.g. 7T) may impact both sensitivity and specificity for the detection of pituitary tumors
- molecular imaging can aid the detection of occult microadenomas and improve delineation between sites of residual or recurrent tumor and postoperative tissue remodelling
- combining molecular imaging with endocrine suppression of tumor activity ('subtraction imaging') has the potential to increase confidence to proceed with pituitary surgery
- the interpretation of pituitary imaging can be enhanced through the use of bespoke pituitary phantoms with improved authenticity
- 3D-printing can benefit both patients and surgeons in planning pituitary surgery.

JM has no relevant relationships to disclose; MG receives speaker honorarium from Ipsen.

Value of Genetic Testing in Managing Pituitary Disease

Fanny Chasseloup and Peter Kamenický

Université Paris-Saclay, Inserm, Physiologie et Physiopathologie Endocriniennes, Assistance Publique – Hôpitaux de Paris, Service d'Endocrinologie et des Maladies de la Reproduction, Centre de Référence des Maladies Rares de l'Hypophyse HYPO, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

Recent advances in diagnostic techniques have improved our knowledge of the molecular bases of pituitary diseases including pituitary adenomas and developmental disorders of the pituitary gland, however, the prevalence of identified causative pathogenic variants remains rather low.

Pituitary adenomas are benign intracanal lesions that can be revealed by local compressive mass effect, distinct hormone hypersecretions, and associated deficiencies in pituitary functions resulting in peripheral endocrinopathies. They are mostly sporadic, but around 5% of them are known to result from germline genetic variations predisposing to pituitary tumorigenesis. In this setting, pituitary adenomas occur as a part of hereditary genetic syndromes, such as multiple endocrine neoplasia and Carney complex, further as familial isolated pituitary adenomas and X-linked acrogigantism. Hereditary pituitary adenomas can also be diagnosed as apparently sporadic lesions, because of *de novo* genetic variations, genetic mosaicism, unknown familial history, or low penetrance.

Congenital hypopituitarism is a rare disease characterized by isolated or combined pituitary hormone deficiencies. Defects of more than 30 genes including those encoding transcription factors involved in pituitary cell differentiation are responsible for this condition, with a large variety of syndromic and non-syndromic presentations. However, the diagnostic yield from genetic testing remains low.

In this session, using a case-based approach, we will review the most prevalent genetic causes of hereditary pituitary adenomas and pituitary hormone deficiencies, interrogate how genetic findings guide clinical thinking and disease management, and discuss appropriate screening strategies in families with members who have a hereditary pituitary disease.

The authors have no relevant relationships to disclose.

HOT TOPICS

Chairs: Pouneh Fazeli and Marily Theodoropoulou

PF receives consulting fees from Xeris Pharmaceuticals, Regeneron Pharmaceuticals, and Quest Diagnostics; MT has no relevant relationships to disclose.

Oxytocin in Hypopituitarism

Elizabeth Lawson

Interdisciplinary Oxytocin Research Program, Neuroendocrine Unit, Massachusetts General Hospital, Boston, Massachusetts, USA

Oxytocin, a hypothalamic hormone that like vasopressin is stored and released from the posterior pituitary gland, has not been well studied in pituitary disease. Our translational work in humans supports preclinical data demonstrating important central and peripheral effects of oxytocin in both sexes, including a role in psychological wellbeing and bone homeostasis. In a proof-of-concept cross-sectional study of men with hypopituitarism, we showed that men with arginine vasopressin deficiency had lower serum oxytocin levels than men with similar anterior pituitary deficiencies and replacement but no arginine vasopressin deficiency, as well as healthy controls. In addition, men with arginine vasopressin deficiency and low oxytocin levels had increased psychopathology compared to the other groups. Lower oxytocin levels in men with arginine vasopressin deficiency were associated with lower bone mineral density and less favorable hip geometry and strength estimates. These data support the concept of a clinically significant oxytocin deficient state in patients with hypopituitarism. To advance our findings to the clinical setting, it will be important to validate diagnostic tests, clinically characterize oxytocin deficiency in both sexes, and investigate the safety and efficacy of oxytocin replacement in patients with hypopituitarism.

EL receives stock options from OXT Therapeutics and research funding and study drugs from Tarix Pharmaceuticals.

Mechanisms Underlying Gigantism in Patients with X-LAG Syndrome

Albert Beckers

University of Liège, Liège, Belgium

Pituitary gigantism is a rare disorder caused by excess of GH/IGF-1 due to GH-secreting lesions, that occurs before epiphyseal closure leading to increased linear growth. Until recently, little scientific research had been specifically dedicated to patients with gigantism. Following works on FIPA and *AIP* gene mutations, it became evident that these patients have more aggressive growth hormone (GH)-secreting pituitary adenomas, and develop the disease much earlier in life (frequently before the end of puberty), thereby permitting the development of gigantism. These works have stimulated scientific, and particularly genetic, studies on patients with gigantism. Over the past two decades several molecular defects that cause GH-secreting pituitary adenomas have been identified, the most recent being X-linked Acro-Gigantism syndrome (X-LAG) in 10 % of gigantism cases. The cause is a duplication involving the gene *GPR101* with massive over-expression of this orphan G-protein coupled membrane receptor in somatotropes. This syndrome includes the most extreme forms of human gigantism (with heights greater than 2m50), such as Julius Koch, alias the giant Constantin (2m59), who died at the age of 30 in 1902.

Hypothalamic GHRH hypersecretion has been observed in some patients. X-LAG is more frequent in females, and associated with early-onset pituitary disease (in most cases during the first year of life) and extremely accelerated linear growth. X-LAG is usually associated with markedly elevated GH and prolactin secretion by mixed pituitary adenomas/hyperplasia. In transgenic Gpr101 mice, elevated GH/prolactin secretion occurred without hyperplasia/tumorigenesis. It remained to be shown how a simple duplication of a gene can lead to such a high expression of the protein. Using Hi-C and 4C-seq, we showed that *GPR101* is located within a topologically associating domain (TAD) delineated by a tissue-invariant border that separates it from other genes and regulatory sequences. In X-LAG patients, the duplication disrupted this border to form a neo-TAD that brings *GPR101* under the control of ectopic enhancers. The new *GPR101*-enhancer interactions are likely to cause the high levels of aberrant expression of GPR101 in these tumors.

These studies on X-LAG have advanced our understanding of the physiology of growth and the pathological hypothalamic-pituitary mechanisms that govern the formation of somatotrope adenomas and development of severe forms of pituitary gigantism.

AB has no relevant relationships to disclose.

Opiates and Pituitary Function

Niki Karavitaki

Institute of Metabolism and Systems Research (IMSR), College of Medical and Dental Sciences, University of Birmingham; Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust; Centre for Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, UK

The naturally occurring alkaloids of opium and the drugs synthesized from it are described as 'opiates', whilst all natural or synthetic chemicals that bind to opioid receptors are included in the term 'opioids'. Opioids are powerful analgesics but they can also be misused due to their euphoric effects. During the last two decades, the use of opioids has increased reaching the dimensions of a global epidemic.

These agents have various effects on the endocrine system with mechanisms not fully elucidated. Hypogonadism is the most common adverse sequelae with variable reported prevalence and its severity depends on the dose, duration of action and type of opioid. Inhibitory action on the hypothalamo-pituitary-adrenal axis has also been described with less clearly defined frequency. The clinical significance of this effect and the necessity of glucocorticoid replacement in many of these cases remain to some extent uncertain. Opioids have also a negative impact on bone health (with reduced bone mineral density and increased fracture risk) and occasionally cause hyperprolactinaemia. Discontinuation or reduction of the opioid or consideration of alternative therapies for pain relief are potential management approaches. Hormonal replacement, especially when the above measures are not practically feasible, is also an option.

Further studies establishing the prevalence of hormonal abnormalities with various regimes, doses and routes of opioids, and also addressing reliably the long-term benefits and risks of hormonal replacement are necessary.

NK has no relevant relationships to disclose.

Artificial Intelligence to Advance Surgical Therapy for Patients with Pituitary Adenoma

Hani Marcus

National Hospital for Neurology and Neurosurgery; UCL Queen Square Institute of Neurology; Wellcome / EPSRC Centre for Interventional and Surgical Sciences; National Institute for Health Research, London, UK

The gold standard treatment for most patients with symptomatic pituitary adenoma is transsphenoidal surgical excision, and this represents among the best examples of minimally invasive surgery in the brain. However, since the introduction of the endoscopic transsphenoidal approach, there has been disappointingly little progress in surgical therapy for pituitary adenoma. Approximately a third of patients with adenoma have residual disease after surgery, and this has not significantly improved over the last 20 years.

In recent years artificial intelligence (AI) has begun to impact clinical care and offer a distinct benefit because they can take advantage of datasets larger than any single clinician could hope to amass over a lifetime of practice. The overall aim of this research is to apply AI to advance surgical therapy for patients with pituitary adenoma: first, to interrogate healthcare records to **reduce the time to diagnosis** for patients with pituitary adenoma; second, to use real-time operative videos to **automatically recognise and augment operative workflows** for patients undergoing surgery for pituitary adenoma; and third, to use healthcare records, radiological imaging, and operative videos to **improve prognostication** for patients that have had surgery for pituitary adenoma.

HM has no relevant relationships to disclose.

GROWTH HORMONE RESEARCH SOCIETY SYMPOSIUM

Chair: Andrew Hoffman

AH receives consulting fees from Ascendis Pharmaceuticals.

Growth Hormone Deficiency in Children

Adda Grimberg

Diagnostic and Research Growth Center, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

Unlike in adults, GHD in children has a very visible presentation; it primarily presents with growth failure or short stature. Patients and families concerned by short stature seek medical care, starting with their primary care provider (PCP) who often refers the patient to a pediatric endocrinologist; sometimes the patient-family bypasses their PCP and goes directly to the endocrinologist. The endocrinologist evaluates the cause of the patient's growth failure/short stature and when appropriate, prescribes GH treatment. For many children, the distinction between a diagnosis of GHD and idiopathic short stature rests on the peak GH response to stimulation testing. In this session, we will discuss disparities in the medical management of short stature leading to GH treatment.

AG receives consulting fees from Ascendis Pharmaceuticals.

Growth Hormone Deficiency in Adults

Andrew R. Hoffman

Stanford University, Palo Alto, California, USA

Growth hormone deficiency (GHD) is characterized by altered body composition, an atherogenic lipid profile, decreased muscle strength and aerobic capacity and a poor quality of life. Adults with GHD suffer from other morbid conditions, including a variety of metabolic, hepatic, renal and mental health conditions. The most common causes of GHD include pituitary and brain tumors, traumatic brain injury, brain irradiation and hypophysitis. In addition, children with organic causes of GHD will continue to have GHD as adults. Nonetheless, it is estimated that fewer than 10% of adults with GHD are diagnosed and treated with GH replacement therapy. We will discuss the proper testing to make the diagnosis of GHD in adults and review the interactions of GH with other hormone replacement therapies. New long-acting GH therapies will also be discussed.

AH receives consulting fees from Ascendis.

This presentation will include discussion of products 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 in the Elderly

Pinchas Cohen

University of Southern California, Los Angeles, California, USA

Growth hormone (GH) physiology during aging represents a complex interconnected metabolic network that challenges simple therapeutic paradigms. On the one hand, the effects of GH lead to a set of actions that could be beneficial in aging individuals: 1) GH secretion (and along with that, IGF-1 levels) fall with age (somatopause), 2) GH builds muscle mass and reduces fat mass, potentially correcting age-dependent changes in body composition, 3) GH builds bone and could reverse aging-associated osteopenia, 4) GH has been reported to alleviate NAFLD which is a common problem in the elderly. On the other hand, major concerns about the use of GH in non-GHD older individuals include: 1) a high rate of side-effects, 2) concerns about the development of malignancies (either directly or through IGF-1 elevations, 3) development of insulin resistance that could lead to overt diabetes, and 4) multiple model organisms associated with manipulation of the GH-IGF system (and limited human data) suggest that increased GH or IGF-1 can lead to reduced lifespan, while inhibition of the GH-IGF axis at multiple sites has been reported to be associated with longevity. Recent discoveries linking the GH-IGF system to healthspan and lifespan promoting agents may be involved in these paradoxical effects of GH, including the inhibition by the GH-IGF system of mitochondrial peptides such as humanin

New approaches to the management of diseases of aging, particularly sarcopenia and frailty, for which no current treatments are available, are needed and potential combination therapies of GH with other approaches that mitigate its potential downsides (such as metformin and dietary restriction) deserve further study.

PC has no relevant relationships to disclose.

INTERNATIONAL PITUITARY SURGEONS' SYMPOSIUM

Chairs: Nelson Oyesiku and Kalmon Post

NO and KP have no relevant relationships to disclose.

Surgical Management of Craniopharyngiomas

Michael Buchfelder

Department of Neurosurgery, University of Erlangen-Nürnberg, Erlangen, Germany

Craniopharyngiomas are rare benign sellar region tumours, which are diagnosed either in childhood or adolescence due to local mass effects on visual pathways, pituitary and hypothalamus, or because of an increased intracranial pressure resulting from obstructive hydrocephalus. Thus, for an individual neurosurgeon it is difficult to acquire expertise particularly in operations of these lesions. The neurosurgeon's challenge is to achieve tumour control without causing major morbidity. There are essentially two different surgical philosophies. Although only gross tumour resection has been proven to provide cure of many patients, the accompanying surgical hazard is substantial. Thus, less aggressive operations with partial or subtotal tumor resection or drainage of cystic portions followed by irradiation have been proposed. They may also relieve the patient's symptoms and the patient may benefit more than from a heroic tumour resection, particularly since to date several variants of radiation therapy are available which may also assist to control tumour progression. The authors' have reviewed the approaches and the strategies employed in children and adolescents, respectively. The use of prognostic scales, derived from preoperative imaging does not only allow to select the most appropriate surgical approach to an individual tumour but also to estimate the risk of uncontrolled gain of weight and other hypothalamic distortions following an operation.

Thus, in summary, in this presentation, the surgical techniques and outcomes of operations in craniopharyngiomas with special focus on the resulting morbidity and mortality are reviewed.

MB has no relevant relationships to disclose.

Outcomes of Surgery in Acromegaly

Juan Fernandez-Miranda

Stanford Brain Tumor, Skull Base, and Pituitary Centers, Stanford University, Palo Alto, California, USA

JF-M will disclose any relevant relationships verbally.

Surgical Strategies in Cushing's Disease

Nelson M. Oyesiku

Dept of Neurosurgery, Dept. of Medicine (Endocrinology), UNC Chapel Hill, Chapel Hill, North Carolina, USA

The optimal treatment of Cushing's Disease is the complete surgical extirpation of the pituitary ACTH secreting adenoma. There are significant steps in planning such surgical treatment and there are nuances in its execution. This presentation will discuss these steps and nuances with the aid of surgical anatomy, video, and case discussion.

NO has no relevant relationships to disclose.

ACROMEGALY

Chairs: Anna Maria Colao and Hidenori Fukuoka

AMC and HF have no relevant relationships to disclose.

IGF-1 Variability and Other Potential Biomarkers of GH Activity

Philippe Chanson

Université Paris-Saclay, Inserm, Physiologie et Physiopathologie Endocriniennes, Service d'Endocrinologie et des Maladies de la Reproduction, Centre de Référence des Maladies Rares de l'Hypophyse, Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

Insulin like growth factor I (IGF-I) measurement is of crucial importance for the diagnosis of acromegaly, as well as for treatment monitoring. As IGF-I levels vary according to age normative data need to be established on large healthy populations (1). This has been achieved in various populations using various IGF-I assays (2-4). In the same large healthy population (911 French healthy adults aged 18–90 years), we demonstrated that the reference intervals of eight commercial IGF-1 assay kits showed noteworthy differences (3, 5). Moreover, when measured in 102 patients with active or treated acromegaly and using calculated IGF-I SDSs based on our normative data, agreement among IGF-I assay methods was only moderate to good (6). These differences in assay performance must be taken into account when evaluating and monitoring patients with GH disorders. This does not mean that an assay is better than another, but that the use of different IGF-I assays for a single patient might affect treatment decisions and dose adjustments, especially when IGF-I levels are borderline. This argues for the use of the same IGF-I assay for a given patient throughout follow-up.

Other factors of variability are sex, ethnicity, insulin sensitivity and diabetic status, nutritional disorders, renal failure, and hepatic insufficiency. Moreover, drugs such as estrogens can also alter IGF-I levels.

Another factor of variability in patients with acromegaly on long-term treatment with long-acting somatostatin receptor ligands (SRLs) could be the time of blood collection for IGF-I measurement after injection. Indeed, we assessed serum IGF-I dynamics and variability in 30 SRL-treated patients by sampling patients weekly during one month after the injection (7). In SRL-treated patients, the IGF-I SDS was higher just before injection than at Day 7 and Day 14 after injection, while it did not significantly vary in cured patients and healthy controls. The IGF-I CV was higher in SRL-treated patients than in cured patients or healthy controls. Among SRL-treated patients, IGF-I CV was higher in "non optimally controlled patients" (i.e., patients with at least one elevated IGF-I value out of four compared with "optimally controlled" patients (for whom all 4 weekly IGF-I SDS values were < 2.0). The latter did not differ from IGF-I CV of surgically cured patients and healthy controls. The measurement at the farthest distance from the SRL injection was the most predictive of patients with non optimally controlled disease, allowing to conclude that in patients treated with long-acting SRLs, IGF-I sampling at the farthest distance from SRL injection is the most informative and best predictor of optimal disease control.

Other potential biomarkers of GH activity such as klotho have been suggested (8-10): their performance compared to IGF-I needs confirmatory studies, particularly in patients with acromegaly of borderline activity.

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PC receives consulting fees from Recordati and Pfizer.

Predicting SRL Responsiveness or Resistance

Diego Ferone

Endocrinology, Department of Internal Medicine & Medical Specialties, IRCCS Ospedale Policlinico San Martino, University of Genova, Italy

The first-generation somatostatin receptor ligands (fg-SRLs), octreotide LAR and lanreotide autogel, are a true milestone of acromegaly medical treatment and may achieve the biochemical control in almost 40% of unselected patients, whereas a variable degree of tumor shrinkage can be recorded in over 60% of them. Therefore, these medications are considered the first-line medical therapy, while the second-generation SRL, pasireotide, although has shown higher efficacy with respect to both biochemical control and tumor shrinkage, is used in second line, in alternative to other medical options (pegvisomant, cabergoline, cocktail therapies), because of the highest degree of glucose imbalance.

Since differently from the past, we have available today many strategies for the medical management of acromegaly patients, there is a strong need to move toward the precision medicine in this field as well. Preclinical, as well as clinical, studies have been already performed or are ongoing for exploring potential biomarkers-based therapy selected not only on the tumor phenotype, but also on the patient characteristics. To predict the response or resistance to SRLs several biomarkers have been investigated with often conflicting results and none of them seems to display a very high accuracy. Apart the somatostatin receptor (SSTR) profiles, considered the best predictor, favoring the selection of responders to both fg-SRLs and pasireotide, other tumor-related biomarkers of response to SRLs include tumor granulation pattern, mutations in the G-protein, AIP, as well as MEN1 genes, Ki-67 expression, SSTR truncated isoforms, E-cadherin, beta-arrestins, and ZAC1 expression, and more recently also miRNAs. Moreover, patient-related predictors involve age, gender, BMI, GH and IGF-I levels, GH response to octreotide test and, interestingly, adenoma signal in MRI T2-weighted sequence.

Intriguing algorithms, as well as potential predictive models for acromegaly management have been developed and proposed in the literature so far. These approaches generally focus mainly on two or more biomarkers as a predictor of response to SRLs. Some combinations of different biomarkers work apparently better than others in predicting different outcomes, and displaying, therefore, positive, or negative, predictive values able to determine the probability of a patient being controlled with SRLs (or other drugs) and supporting the choice of the most appropriate therapy, or even of a specific sequential strategy.

With the increased availability of new medications, as well as of innovative formulations of SRLs, the personalized treatment of acromegaly has the potential to increase control rates in this setting, however, further investigations are warranted, possibly prospective studies addressing the utility and power of the biomarkers and models settled at this scope.

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Experimental Medical Therapies

A.J. van der Lely

Division of Endocrinology, Dept. of Medicine, Erasmus University MC, Rotterdam, The Netherlands

Treatment options of acromegaly include surgery, medical therapy, and/or radiation therapy. Surgery is usually the preferred treatment; the smaller the tumor, the more likely surgery will be curative. If surgery is contraindicated or not curative, somatostatin analogues, dopamine agonists or GH receptor antagonists may be used. Long-acting somatostatin analogs, both the first- and second-generation ones, are administered as monthly injections. Upcoming are the oral somatostatin analogs. The first kid-on-the-block is MYCAPSSA® octreotide. MYCAPSSA® (a delayed-release oral capsule) is the first and only FDA-approved oral somatostatin analog for appropriate patients with acromegaly, providing effective and consistent biochemical control, while (according to the company) freeing patients from the burden of injections. MYCAPSSA is powered by patented Transient Permeability Enhancer (TPE®) technology. It maintained normal IGF-I levels in most patients who switched from injectable SSAs. BID oral dosing leads to consistent biochemical control in a significant proportion of subjects in the registration studies. Paltusotine is another new oral SSA analog. It is an investigational, potential first-in-class, oral nonpeptide sst2 agonist, currently developed in phase 3. When approved it will join MYCAPSSA when it comes to new ways of administration SSAs.

To date, pegvisomant is the only available GH receptor antagonist. However, the group of John Kopchick recently presented the design, synthesis, and characterization of a 16-residue peptide (site 1-binding helix [S1H]) that inhibits hGH-mediated STAT5 phosphorylation in cultured cells. Other research groups and companies also are active in developing new GHRAs. For instance, Amolyt

Pharma SA recently reported positive preclinical data on their compound AZP-3813, a 16 amino acid, bi-cyclic peptide antagonist of the hGH receptor. Cimdelirsen, formerly known as IONIS-GHR-LRx, is a ligand-conjugated (LICA) investigational antisense medicine designed to reduce the production of the growth hormone receptor (GHR) to decrease the circulating level of IGF-I. Apparently the modification of GH activity via blocking the GH-receptor has become a rapidly moving area.

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Acromegaly and Bone

Melin Meliha Uygur

Institute of Endocrine and Metabolic Sciences, Università Vita-Salute San Raffaele, and Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Ospedale San Raffaele, Milan, Italy; Department of Endocrinology and Metabolism Disease, School of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey

Acromegaly is a rare, chronic endocrine disease usually caused by growth hormone (GH) secreting pituitary adenoma; associated with a wide range of systemic complications leading to increased mortality. Vertebral fractures (VFs) are one of the acromegaly complications occurring despite normal mean bone mineral density (BMD) values and associated with a high risk of subsequent fracture, decreased survival, and low quality of life (QOL)[1].

Effects of GH hypersecretion on vertebral fractures

The median prevalence of VFs was 40%, with a fracture risk threefold to eightfold higher in acromegaly patients than in control subjects. VFs were more frequent in active disease vs. controlled disease, males vs. females, and hypogonadal vs. eugonadal patients [2]. Incident VFs (i-VFs) developed in 42% of patients with acromegaly during a 3-year follow-up, and i-VFs were significantly higher in patients with active disease than controlled disease. The rate of VFs was related to baseline disease status and duration of active disease; hypogonadism and preexisting VFs were shown to influence the fracture risk only in patients with controlled acromegaly but not in those with active disease [2]. VF progression was also documented in 20% of biochemically controlled patients, especially in men and in cases with greater than two VFs at baseline in patients with acromegaly at study entry [3]. More data on i-VFs in patients with active acromegaly undergoing different medical therapies reported a higher i-VFs in patients with active disease regardless of the therapeutic approach[4].

A recent study showed a high prevalence of radiological thoracic VFs associated with higher presurgical serum random GH levels in a large cohort of recently diagnosed acromegaly patients [5]. The data supported that VFs are a relatively early event in the natural history of the disease and confirm the detrimental role of GH excess on bone. i-VFs occurred in 34.3% of acromegaly patients in a recent study which confirmed for the first time that patients with a diagnostic delay >10 years had 1.5-folds increased risk of developing i-VFs [6]. Early diagnosis and treatment of acromegaly may be effective in protecting bone complications. However, this may not be sufficient to stop the progression of osteopathy [4].

Assessment of bone quality: TBS, HR-pQCT, 3D Shaper, HR-CBCT, BMSi

Studies showed lower trabecular bone score (TBS) in patients with acromegaly without any significant difference in BMD[7].

High-resolution peripheral quantitative computed tomography (HR-pQCT) studies showed significant associations between altered bone microarchitecture and either gonadal status or activity of the disease in patients with acromegaly and supported that compromised bone microstructure may occur regardless of gonadal status[7]. The concept was reinforced by a study that reported not only deterioration of the trabecular microstructure of the radius in eugonadal patients; but also provided important novel insights into increased porosity and impaired strength of cortical bone [8].

Acromegaly patients with vertebral fractures had significantly lower bone volume/trabecular volume ratio, greater mean trabecular

separation, and higher cortical porosity vs. nonfractured patients, without statistically significant differences in mean trabecular thickness and cortical thickness in High-resolution cone-beam CT (HR-CBCT) [9]. The application of microindentation showed that patients with well-controlled acromegaly had significantly lower bone material strength index (BMSi) values than healthy controls. Cortical bone strength decreased in acromegaly that could reflect persistent alterations in the material properties of cortical bone even after cessation of the disease[10].

The effect of medical therapies of acromegaly on skeletal fragility

The specific effect of medical therapies of acromegaly on skeletal fragility is still not apparent due to the limited data[4]. A cross-sectional study evaluated the prevalence and determinants of VFs in a selected series of difficult acromegaly patients undergoing pegvisomant (PegV) treatment showed that VFs may frequently occur in patients under treatment with PegV, in relationship with persistently active disease and coexistence of untreated hypogonadism[11]. A longitudinal retrospective study showed that patients with biochemically active disease treated with Pasireotide LAR had lower risk of i-VFs vs. those treated with PegV [12].

Novel bone markers in acromegaly:

Wnt signaling pathway is one of the mechanisms involved in bone fragility. Sclerostin (SOST) and Dickkopf-1 (DKK-1) are osteocyte-produced mediators that act as antagonists of the Wnt signaling [13]. The impact of acromegaly on parameters of bone microarchitecture and inhibitors of Wnt signaling evaluated in a group of premenopausal women without any pituitary deficiency. The study identified impairment of trabecular bone microarchitecture, low SOST, and higher DKK-1 levels. A positive correlation between DKK-1 levels and cortical porosity highlighted DKK-1 as a potential biomarker of compromised cortical bone[13]. Several research groups also investigated SOST levels in relationship to disease activity and fractures in acromegaly, showing contradictory results, and inconsistent associations between SOST and GH/IGF-1 levels [14-16]. Due to these conflicts, Classen et al. asserted a hypothesis that SOST levels might differ between three different phases (active, early remission, and chronic remission) of osteopathy in acromegaly[15]. This interpretation might explain the persistent fracture risk in acromegaly patients after remission contrary to other pituitary disorders like Cushing disease. Nevertheless, no association found between SOST levels and VF presence[16].

CONCLUSION:

The morphometric vertebral fracture assessment (VFA) represents the cornerstone of the skeletal investigation in patients with acromegaly and should be assessed both at diagnosis and during follow-up, particularly in those that already experienced VFs. Bone quality evaluation has been applied to investigate bone microarchitecture as the gold standard tool, nonetheless, their high cost, huge amount of ionized radiation and reduced availability make it more suitable for the research scope. New bone markers must be validated and confirmed in independent studies before reaching application in acromegaly.

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Acromegaly Registries

John Ayuk

University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Disease registries are databases containing information about people diagnosed with a specific disease. They provide health care professionals and researchers with information about people with certain conditions, thereby increasing understanding of that condition. With rare conditions, disease registries allow pooling of data and achievement of sufficient sample sizes to provide meaningful clinical and research outcome data. Over the years a number of regional, national and international acromegaly registries have provided crucial evidence which has helped to overcome the knowledge gap which is inherent with rare conditions. Data from these registries have contributed to the knowledge of epidemiology, natural history, diagnosis and management of acromegaly, and provided the basis for evidence-based acromegaly guidelines. This lecture will explore key messages and benefits derived from some of these registries, as well as the challenges involved in establishing and maintaining them.

JA has no relevant relationships to disclose.

ORAL PRESENTATIONS/YOUNG INVESTIGATOR AWARDS

Chair: Jérôme Bertherat and Mercedes Piñeyro

The authors have no relevant relationships to disclose.

P1

Epigenetic Control of Adamantinomatous Craniopharyngiomas

Clarissa Silva Martins[1]; Junier Marrero-Gutiérrez[1]; Ana Carolina Bueno[2], Fernanda Borchers Coeli-Lacchini[1]; Gabriel Henrique Marques Gonçalves[1]; Jorge Guilherme Okanobo Ozaki[3#]; Danillo C. de Almeida e Silva[4]; Eduardo Wildemberg[5]; Ximene Lima da Silva Antunes[5]; Antônio Carlos Santos[6]; Helio Rubens Machado[7]; Marcelo Volpon dos Santos[7]; Ayrton Custodio Moreira[1]; Monica R Gadelha[5]; Ricardo Zorzetto Nicoliello Vêncio[4]; Sonir Roberto R. R. Antonini[2]; Margaret de Castro[1]

Departments of [1]Internal Medicine, [2]Pediatrics, [3]Medical Imaging, [6]Hematology, and Oncology, [7]Surgery and Anatomy, Ribeirao Preto Medical School, University of São Paulo, Ribeirao Preto, SP, Brazil; [4]Department of Computation and Mathematics Biology, Faculty of Philosophy, Sciences and Letters at Ribeirao Preto, University of São Paulo, Ribeirao Preto, SP, Brazil; [5]Neuroendocrinology Research Center/Endocrinology Section, Medical School and Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; # Current affiliation: JGOO: Sonimed Medicina Diagnostica, Campo Grande, Brazil

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Introduction: There are, to date, no studies addressing the methylation pattern in adamantinomatous craniopharyngioma (ACP). Thus, the objective of this study was to identify differential methylation signatures in ACPs and their association with clinical presentation and outcome.

Materials and Methods: We analyzed 35 ACP patients (54% male; 18.1, 2- 68 years with 66% diagnosed before 18 years of age). Clinical, biochemical and pathology data were retrospectively collected. *CTNNB1* mutations and methylation profile (MethylationEPIC Array-Illumina) were analyzed in tumoral DNA. Unsupervised Hierarchical Cluster Analysis (UHCA) using Euclidean distance as metric, Ward D2 as grouping, and Bootstrap, as robustness check, were applied to Quantile normalized data. Fisher›s and Mann–Whitney–Wilcoxon›s tests were applied to interpret and cross correlate clusters with external clinical information.

Results: UHCA revealed two clusters, aCP1 and aCP2, with distinct methylation signatures and 100% bootstrap support. aCP2 cluster (n=17) was enriched with *CTNNB1* mutated aCPs (p=0.0006). aCP1 and aCP2 exhibit 4,091 differently methylated probes (|log2 fold change|>1 and FDR p-values $<10^{-7}$), corresponding to 1,866 genes, being 17% located in regulatory regions. There was a significant association between *CTNNB1* mutated aCPs and hypermethylation in *CTNNB1* 3'UTR (p<0.001). Interestingly, a higher level of hypermethylation in the 3'UTR of the WT *CTNNB1* was associated with E-cadherin related genes involved in cell migration and tumor invasion. Except for greater tumor volume in cluster aCP2 (9.5 vs 24.1 cm3, p = 0.04), there was no association between the methylation profiles and demographic or clinical presentation features.

Conclusion: aCPs present two distinct methylation signature clusters revealed by UHCA. One of these clusters is significantly enriched by *CTNNB1* mutated aCPs. In WT *CTNNB1* aCPs, hypermethylation in the 3›UTR of genes associated with cell migration and tumor invasion was observed. These new findings offer new insights on the pathogenesis of aCP.

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P2

Accuracy of Biochemical Tests Differentiating Neoplastic from Non-neoplastic Hypercortisolism in Cushing's Syndrome: A Systematic Review and Meta-analysis

José Miguel Hinojosa-Amaya[1]; Fernando Díaz González-Colmenero[2]; Alejandro Salcido-Montenegro[2]; Carolina Quintanilla-Sánchez[2]; Pablo José Moreno-Peña[2]; Dulce María Manzanares-Gallegos[2]; Luis Fernando Gutiérrez-Dávila[2]; Patricia Lizeth Castillo-Morales[2]; Mariano García-Campa[2]; Elena V. Varlamov[3]; José Gerardo González-González[1,2]; René Rodriguez Gutiérrez[*1,2]; Maria Fleseriu[*3]

[1]Endocrinology Division, Department of Internal Medicine, University Hospital "Dr. José E. González", Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo León, Mexico; [2]Plataforma INVEST Medicina UANL-KER Unit Mayo Clinic (KER Unit Mexico), Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, Mexico; [3]Departments of Medicine (Endocrinology) and Neurological Surgery, and Pituitary Center, Oregon Health & Science University, Portland, Oregon, USA
** Co-senior authors*

Background: Cushing's syndrome due to neoplastic endogenous hypercortisolism (NEH) is associated with increased morbidity and mortality, while non-neoplastic hypercortisolism (NNH), aka "Pseudo-CS", is a physiological stress adaptative response. Dexamethasone-suppressed CRH test (Dex-CRH) has been the study of choice to rule-out NNH. CRH worldwide unavailability prompts alternative tests' use: Desmopressin (DDAVP) stimulation test, midnight serum cortisol (MSC), and late-night salivary cortisol (LNSC).

Objective: To estimate pooled diagnostic accuracy of Dex-CRH, DDAVP, MSC, and LNSC for diagnosis of NEH versus NNH.

Methods: Systematic review (PROSPERO: CRD42020206281) of studies on confirmed NEH and NNH. Expert librarian search (Scopus, Web of Science, Medline, Embase, Pubmed). Pilot (aiming κ0.70), data extraction, and quality evaluation (QUADAS-2) in

duplicate independently with conflict resolution. Statistics: R software (v4.0).

Results: 4624 records without duplicates; 367 after abstract screening; 47 eligible, 25 with extractable data. Total patients 1883 (NEH 976; NNH 907). Diagnostic accuracy for Dex-CRH, DDAVP, MSC, and LNSC, respectively, was: Sensitivity 91% (95%CI 87-94; $I^2$0%), 87% (81-91; $I^2$34%), 91% (85-94; $I^2$65%), 78% (66-86; $I^2$54%); Specificity 82% (73-88; $I^2$50%), 90% (85-94; $I^2$15%), 80% (70-88; $I^2$70%), 88% (83-92; $I^2$36%); diagnostic odds ratio (DOR) 88% (83-92; $I^2$36%), 75.79 (37.87-151.7; $I^2$18%), 69.72 (33.95-143.16; $I^2$39%), 72.22 (26.12-199.67; AUC 0.922, 0.856, 0.939, 0.796.

Discussion: Dex-CRH and MSC had highest sensitivity with similar accuracy and AUC, while DDAVP has the highest specificity, second to Dex-CRH in DOR. Interestingly, LNSC has the lowest performance despite measuring cortisol at bedtime, similar to MSC; variability of chosen cutoffs and significant heterogeneity in studies of both tests could be the culprit.

Limitations: risk of overestimating accuracy with Youden's index use in some studies, and lack of consistent "standard" cutoff reporting.

Conclusion: DDAVP test is a good alternative to Dex-CRH test or MSC. Though a good screening and recurrence test, LNSC had the lowest accuracy and highest heterogeneity for differential diagnosis of NNH.

EV's institution receives research support from Recordati; MF's institution receives research support from Crinetics, Recordati, Sparrow and Xeris and she receives consulting fees from HRA Pharma, Recordati, Sparrow and Xeris; the other authors have no relevant relationships to disclose.

P3

Post-Operative Fluid Restriction Prevents Hyponatremia and Readmissions After Pituitary Surgery

Julia Chang[1], Darlene Veruttipong[2], Olivia Chu[3], Erin Wipff[3], Victoria Gates-Bazarbay[3], Samantha MR Kling[2], Juan Carlos Fernandez-Miranda[4]

Division of Endocrinology, Gerontology, and Metabolism, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA[1]; Division of Primary Care and Population Health, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA[2]; Neuroscience Health Center, Stanford Health Care, Palo Alto, CA, USA[3]; Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA, USA[4]

Objective: Delayed hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion is the most common cause of readmission after pituitary transsphenoidal surgery (TSS). Post-operative fluid restriction (FR) after discharge may effectively reduce hyponatremia and related readmissions. The aim of this study was to assess the effectiveness of FR after TSS.

Methods: We compared post-operative day (POD) 8 hyponatremia and related readmission rates pre- and post- FR protocol implementation at our institution. Pre-FR (July 1, 2018-March 15, 2020) post-TSS patients were instructed to drink *ad lib* or to thirst on discharge. Post-FR (March 16, 2020-December 31, 2022) post-TSS patients were routinely provided education and documentation on an outpatient protocol that recommended 1 liter/day FR from POD 3-5 to POD 8-10. Serum sodium was assessed at POD-8 for all patients. Patients hospitalized for >5 days after surgery, had untreated adrenal insufficiency, or had pre-existing AVP deficiency were excluded.Results: The average POD-8 sodium level was lower in the 115 patients in the pre-FR cohort than the 216 patients in the post-FR cohort (135.8±6.7 vs. 138.1±4.4 mEq/L; Wilcoxon-Mann-Whitney test p=0.0081). POD-8 hyponatremia (Na ≤134 mEq/L) occurred in a lower proportion of patients post-FR (15.0%; 32/214) than pre-FR (28.9%; 30/104) (Chi-Square test p=0.0033). Similarly, severe hyponatremia (Na ≤124 mEq/L) occurred in a lower proportion of patients post-FR (1.4%; 3/214) than pre-FR (8.7%; 9/104) (Fisher test p= 0.01). Only 1.4% (3/216) of patients were readmitted post-FR compared to the 8.7% (10/115) pre-FR (Fisher test p=0.0020).

Conclusion: Our retrospective evaluation showed that implementation of post-TSS FR protocol significantly decreased hyponatremia by nearly 50% and readmissions by over 80% compared to the prior standard of care of drink *ad lib* or to thirst. FR should be considered standard-of-care for most patients after pituitary surgery to reduce hyponatremia and readmission burden to both patient and healthcare system.

The authors have no relevant relationships to disclose.

P4

^{68}Ga-DOTATOC PET/CT in Localization of ACTH-Secreting Pituitary Tumors in the Patients with Cushing's Disease

Kyungwon Kim; Eun Jig Lee; Cheol Ryong Ku

Endocrinology, Institute of Endocrine Research, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

Objective: This study aimed to determine the value of ^{68}Gallium-DOTATOC positron emission tomography/computed tomography (^{68}Ga-DOTATOC PET/CT) in localizing adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas.

Methods: We enrolled 30 patients with Cushing's disease (CD) who underwent ^{68}Ga-DOTATOC PET/CT, pituitary magnetic resonance imaging (MRI), and bilateral inferior petrosal sinus sampling (BIPSS) before transsphenoidal adenomectomy (TSA). We compare three kinds of modalities for localization based on the tumor location identified by surgeons following TSA.

Results: Twenty-five patients showed ^{68}Ga-DOTATOC uptake in their pituitary glands on PET/CT. Median age was 34(15-68) years and 25 of 30 patients showed 68Ga-DOTATOC uptake in PET/CT. Median age (30 vs. 51 years), pre-operative ACTH (84.30 vs. 50.87 pg/ml), pre-operative cortisol (20.60 vs. 17.90 pg/ml), and tumor size on MRI (7.75 vs. 5.00 mm) were not differ according to the presence or absence of DOTATOC uptake. MRI showed a success rate of 90.00% for localization compared to 76.67% with ^{68}Ga-DOTATOC PET/CT and 68.00% with BIPSS (P=0.127). The ACTH level in the successful localization group was significantly higher than those in the failed group (84.41 vs. 37.26 pg/ml, P=0.001). The ACTH level was statistically significant in predicting the odds of successful localization using ^{68}Ga-DOTATOC PET/CT (P=0.013). The area under the curve was measured to be 0.932 with a cut-off of 53.86 pg/ml for ACTH levels to determine successful localization. Pre-operative ACTH levels above 53.86 pg/ml showed the best diagnostic accuracy in predicting the success of localizing adenomas (sensitivity, 91.3%; specificity, 85.7%).

Conclusions: The success rates for localizing tumors by ^{68}Ga-DOTATOC PET/CT were not statistically different from those of MRI, regardless of the tumor size. Serum ACTH level is a favorable predictor for the successful localization of corticotroph adenomas. Thus, ^{68}Ga-DOTATOC PET/CT could be a promising approach to improving diagnostic success compared with MRI alone for CD.

The authors have no relevant relationships to disclose.

P5

Comparative Outcome of Surgical Versus Non-Surgical Treatment of Pituitary Apoplexy: Results from a Multi-Center International Observational Study of Pituitary Apoplexy

Adam N. Mamelak[1]; Andrew S. Little[2]; Paul A. Gardner[3]; João Paulo Almeida[4,5]; Fred Gentili[5†]; Pablo Recinos[6]; Pranay Soni[6]; Varun Kshettry[6]; John A. Jane, Jr.[7]; Garni Barkhoudarian[8]; Daniel F. Kelly[8]; Robert Dodd[9]; Debraj Mukherjee[10]; Zachary C. Gersey[10]; Noriaki Fukuhara[11]; Hiroshi Nishioka[11]; Eui-Hyun Kim[12]; Claude-Fabien Litré[13]; Elliott Sina[1]; Mia W. Mazer[1]; Vivien Bonert[14]

[1]Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, California USA; [2]Department of Neurosurgery, Barrow Neurological Institute, St Joseph's Medical Center, Phoenix, Arizona USA; [3]Department of Neurosurgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania USA; [4]Department of Neurosurgery, Mayo Clinic, Jacksonville, Florida USA; [5]Department of Neurosurgery, University of Toronto Health System, Toronto, Ontario Canada; [6]Department of Neurosurgery, Cleveland Clinic Foundation, Cleveland, Ohio USA; [7]Departments of Neurosurgery and Pediatrics, University of Virginia Medical Center, Charlottesville, Virginia USA; [8]Pacific Neuroscience Institute, St John's Medical Center, Santa Monica, California USA; [9]Department of Neurosurgery, Stanford University Medical Center, Stanford, California USA; [10]Department of Neurosurgery, Johns Hopkins University, Baltimore, Maryland USA; [11]Department of Hypothalamic and Pituitary Surgery, Toranomon Hospital, Tokyo, Japan; [12]Department of Neurosurgery, Yonsei University College of Medicine, Seoul, Korea; [13]Department of Neurosurgery, CHU de Reims, Reims, France; [14]Pituitary Center, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA; †In Memoriam

Introduction: Pituitary Apoplexy (PA) has traditionally been treated as a neurosurgical emergency. However, several retrospective single-institution studies have demonstrated that nonsurgical treatment is equally effective selected patients. We conducted a multicenter international observational study to survey contemporary practices and outcomes for PA. **Methods:** Patient demographics, treatment type, tumor characteristics, frailty, quality of life, headache, and outcomes were tracked in a HIPPAA compliant cloud-based registry. Treatment was determined by the physician team at each center. Groups were then analyzed to compare surgical versus non-surgical treatment outcomes at 3 months. We further compared between "early" (1-4 days after symptom onset) versus "late" (>4 days) surgery groups. **Results:** 100 consecutive PA patients from 8 hospitals in the US, 1 in Canada, 2 in Asia, and 1 in France were enrolled over 4 years. Adequate data for analysis was available on 97 patients (97%) (66 surgical and 31 medical). Pre-PA clinical features including

age, sex, BMI, morbidities, medications, and fragility were no different between groups (p>.05). Similarly, presenting symptoms, hormonal deficits, opthalmoparesis, radiographic findings, and tumor size were not different between groups. Severe temporal visual field deficit was more common in the surgical group (33% v 10%, p=0.017). Altered level of consciousness was rare in both groups (10% surgical, 6.7% medical, N.S.). Outcomes at 3-6 months were similar between groups, including hormonal, visual, oculomotor and QOL scores (p =0.4-p=0.9 range). Timing of surgery did not correlate with presenting symptoms or outcome at 3 months. **Conclusion:** In patients without severe visual field deficits, this first-ever multi-center international observational study of PA indicates that patients managed surgically and medically have similar outcomes. The timing of surgery did not correlate with outcomes. Despite more patients presenting with severe visual deficits undergoing surgery, it remains unclear if surgery significantly improved outcomes at 3 months.

The authors have no relevant relationships to disclose.

P6

Age-Dependent Risks and Benefits of Surgical Intervention for Pituitary Adenomas: Long-Term Surgical Outcomes at Our Institution

Yuki Shinya[1]; John L.D. Atkinson[1]; Garret Choby[2]; Irina Bancos[3]; Caroline J. Davidge-Pitts[3]; Justine S. Herndon[3]; Dana Erickson[3]; Sukwoo Hong[1]; Charbel Moussalem[1]; Jamie J. Van Gompel[1]

[1]Department of Neurologic Surgery, Mayo Clinic, Minnesota, USA; [2] Department of Otolaryngology-Head and Neck Surgery, Mayo Clinic, Minnesota, USA; [3] Division of Endocrinology, Diabetes, and Nutrition, Mayo Clinic, Minnesota, USA

Objective: Since patients with pituitary adenomas face variable risks of complex symptoms due to adenoma mass or hormone overproduction, it is essential to identify patient populations who benefit most from intervention. This study aimed to explore clinical behavior of adenomas and long-term outcomes of patients following endonasal transsphenoidal surgery (ETS) considering age stratification.

Methods: This retrospective study enrolled 436 adenoma patients who underwent ETS with a median follow-up period of 58 months. The outcomes included progression-free survival rates (PFSs), neurological, and endocrine outcomes. Age-stratified analyses using Kaplan-Meier and Cox proportional hazard analysis were performed. Patients were classified into four age groups: <49, 50-59, 60-69, and ≥70 years old. The study was approved by the institutional review board.

Results: Age-stratified analysis showed a significant correlation between age and PFSs in non-functioning adenomas (the 5- and 8-year PFSs were 61.4% and 48.3% in <49 group, 79.1% and 79.1% in 50-59 group, 85.8% and 82.6% in 60-69 group, and 88.1% and 88.1% in ≥70 years old group, log-rank test; p = 0.028), but not in functioning adenomas. Multivariable analysis demonstrated that age (HR, 1.04; 95% CI, 1.02-1.06; p = 0.001) and gross total resection (HR, 9.81; 95% CI, 3.46-27.78; p = 0.001) were significantly associated with better PFSs in non-functioning adenomas. Multivariable analysis also demonstrated that only age was associated with postoperative improvement for hypogonadism in non-functioning adenomas (HR, 0.13; 95% CI, 0.01-1.18; p = 0.003), postoperative worsening for hypogonadism in growth hormone-producing adenomas (HR, 19.88; 95% CI, 1.37-288.04; p = 0.028), and prolactinomas (HR, 8.04×10^8; 95% CI, 0.00-N/A; p = 0.018). Other neurological and endocrine outcomes did not significantly differ among age groups.

Conclusions: Our analysis demonstrated that age at ETS is significantly associated with PFSs in non-functioning adenomas and hypogonadism improvement. Neurological outcomes were satisfactory across all age groups.

The authors have no relevant relationships to disclose.

ROLE OF PATIENT SUPPORT GROUPS IN PITUITARY CLINICAL CARE AND RESEARCH

Chairs: Eliza Geer and Laurence Katznelson

EG and LK have no relevant relationships to disclose.

Acromegaly Community

Jill Sisco

Acromegaly Community: Our mission is to provide an emotional and communal support network for people touched by Acromegaly. We support our patients and empower them to be their best advocates in navigating through the challenges they encounter.

Our website, www.acromegalycommunity.org, provides a central location for medical information on issues including:

- Surgery
- Medication
- Radiation
- Post diagnosis support

Most importantly, we work to provide a network of emotional support for our Acromegaly patients, their friends and family. We educate through regional and international meetings and webinars. Our belief is that if you give someone a fish, you feed them for a day, but if you teach them to fish you feed them for a lifetime. This same analogy guides our philosophy educating our patients. To educate is the most powerful thing a patient can do to help themselves.

JS has no relevant relationship to disclose.

CSRF – Cushing's Support Research Foundation

Leslie Edwin

The Cushing's Support & Research Foundation (CSRF) was incorporated in 1995 to be a "missing piece of the puzzle" for patients when Founder Louise Pace was compelled to create the peer support network she needed that did not exist as she struggled with her own recovery. She knew early on that the mission would grow, and she made sure to professionalize from the very beginning by recruiting a robust Medical Advisory Board and registering as a 501c3 non-profit organization. Today CSRF is a globally-accessed resource dedicated to giving and encouraging holistic support and patient representation wherever decisions are made about care and treatment options. CSRF plans to launch a US Patient Registry and Global Member Journey Mapping Project in Autumn 2023 and looks forward to celebrating 30 years of changing the game in 2025. President Leslie Edwin will share recent patient trends, accomplishments, and upcoming projects in her presentation.

LR has no relevant relationships to disclose.

WAPO - World Alliance of Pituitary Organizations

Leslie Edwin

The World Alliance of Pituitary Organizations (WAPO) was born from a series of international patient advocacy meetings in 2012-2014 with a mission to unite the global pituitary community in work toward better education, treatment, and care for all patients. Member organizations run a spectrum between well-established groups with thousands of members to new start-ups with just a couple of passionate advocates and few resources. Sharing best practices via collaborative projects and the annual Summit meeting offers a sense of equality and encourages focus on work where it can be most useful. As the WAPO network gets larger and stronger, we are able to reach more patients in countries where there are often zero identified specialists who can diagnose, treat, and provide aftercare for difficult pituitary disorders. Board Member Leslie Edwin will share challenges, triumphs, and upcoming opportunities in her presentation.

LR has no relevant relationships to disclose.

CLOSING PLENARIES

Chairs: Andrea Giustina and Shlomo Melmed

AG receives consulting fees from Ipsen, Pfizer, and Recordati; SM has no relevant relationships to disclose.

Pituitary Adenoma Nomenclature: Consensus Statement

Ken K.Y. Ho

The Garvan Institute of Medical Research, St. Vincent Hospital and the UNSW Sydney, Australia

The 2022 5th edition of the WHO Classification of Endocrine Tumours and of Central Nervous System Tumours reclassify pituitary adenomas (PAs) as neuroendocrine tumors (NETs), conferring a foreboding oncology label to neoplasms that are overwhelmingly benign. The Pituitary Society convened an interdisciplinary international workshop (PANOMEN 2) to address the merit and the clinical implications of this pathologic classification by reviewing developmental and molecular biology, histopathology, and epidemiology of PAs and the clinical implications of the classification change. Although PAs and NETs exhibit some morphological and ultrastructural similarities, their developmental origins differ. Unlike NETs, PAs are highly prevalent yet typically indolent. Malignancy of primary pituitary neoplasms has never been reported at first diagnosis in contrast to up to 50% of NETs. The classification change to NET does not advance mechanistic insight, does not align with the favorable prognosis of PAs, and confers an oncology label, potentially leading to overtreatment as well as patient consternation and anxiety. Many factors independent of histopathology provide mechanistic insight and influence the prognosis and treatment of PAs. PANOMEN 2 recommended the development of a comprehensive classification that integrates clinical, genetic, biochemical, radiologic, pathologic, and molecular information for all anterior pituitary neoplasms including the majority that do not require surgery.

KH has no relevant relationships to disclose.

Pituitary Tumors Centers of Excellence

Felipe F. Casanueva

Molecular Endocrinology Group, Instituto de Investigacion Sanitaria (IDIS), Complejo Hospitalario Universitario de Santiago (CHUS/ SERGAS). Santiago de Compostela University. Spain

In the pursuit of healthcare excellence, the Pituitary Society generated a set of criteria for developing a Pituitary Tumors Center of Excellence (PTCOE). The goal was to propose uniform criteria among centers dealing with pituitary tumors to enhance patient care. The need for a PTCOE arise because only a team of highly trained neuroendocrinologists plus highly experienced neurosurgeons trained in transsphenoidal procedures can reach therapeutic success, minimize treatment complications, and reduce future relapses.

Although a detailed procedure needs to be fully developed, it is probable that the Pituitary Society must undertake future methods of accreditation or identification of PTCOE. It is envisioned that any accreditation procedure would be based on at least two steps. The final one would be an "in situ" validation of the structure and outcomes of any candidate organization. However, the initial steps must be based on self-reported data. For that reason, to select the relevant information for such initial screening is needed. To this purpose a collection and evaluation of self-reported activity of several worldwide recognized pituitary tertiary centers was undertaken an ad hoc prepared database was distributed to 9 Pituitary Centers chosen by the scientific committee among the centers with best reputation worldwide which agreed to provide activity information derived from registries related to the years 2018-2020.

This effort internally validated by ad hoc reviewers allowed for the transformation of previously formulated theoretical criteria for the definition of a PTCOE to precise numerical definitions based on real-life evidence. The application of a derived objective model can be used for future accreditation of pituitary centers as PTCOEs. As these proposed criteria are transparently discussed and accepted by the scientific community, the managing of the accreditation process by the Pituitary Society as an accrediting body would need to be established through a well-balanced cost-efficacy analysis to assure high standards, objectivity and transparency leading to the development of a rapid, easy, and yearly updated procedure.

FC has no relevant relationships to disclose.

POSTER PRESENTATIONS
CRH/ACTH/CUSHING'S

P7

Autoimmune Disorders Associated with Surgical Remission of Cushing's Disease

Dennis Delasi Nyanyo[1]; Masaaki Mikamoto[2]; Francesca Galbiati[1]; Ilan Remba-Shapiro[1]; Kevin J Bode Padron, Sarah Schoenfeld[3]; Pamela Jones[2]; Brooke Swearingen[2]; Lisa B. Nachtigall[1]

[1]The Neuroendocrine Unit, Department of Medicine, Massachusetts General Hospital Harvard Medical School Boston, Massachusetts, USA; [2]The Department of Neurosurgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [3]The Division of Rheumatology, Department of Medicine, Massachusetts General Hospital Harvard Medical School Boston, Massachusetts, USA

** These authors contributed equally to this work*

Following remission, a subset of patients with Cushing's Disease (CD) develop autoimmune disease, but limited information is available regarding this association. In this study, we sought to determine the incidence of autoimmune disorders in CD following surgical remission, characterize the clinical presentation and identify associated risk factors.

We evaluated the incidence of autoimmune disease within 3 years post-operatively in adult patients who had transsphenoidal surgery (TSS) for CD vs. non-functioning pituitary adenomas (NFPA). The CD group (N=173) included patients with pathologically confirmed ACTH-secreting adenomas with surgical remission. The control group (N=83) included age- and sex-matched patients who had TSS for NFPAs. Continuous variables were reported as median and interquartile range and compared using Mann-Whitney U test. Categorical variables were compared using Fisher's exact or chi-square test. 2-tailed $p \leq 0.05$ was considered statistically significant.

Compared to controls, the incidence of all postoperative autoimmune disease was higher in the CD group (11.6% vs. 2.4%, p=0.016), who also had a higher incidence of new-onset autoimmune disease (9.3% vs. 1.2%, p=0.015). The CD group had significantly lower nadir serum cortisol levels after TSS (median 1.0 μg/dl vs. 8.7 μg/dl, $p<0.001$). In patients with CD who developed autoimmune disease compared to those with CD who did not, the pre-operative 24-hour urine free cortisol (UFC) ratio (UFC/upper normal range) was lower (median 2.1 vs. 3.5, p=0.039), the prevalence of prior history of autoimmune diseases was higher (50.0% vs. 22.2%, p=0.013), and there was a trend towards higher prevalence of family history of autoimmune disease (40.0% vs. 21.6%, p=0.091).

Conclusion: Patients who achieved surgical remission for CD have a higher incidence of autoimmune disease compared to age- and sex-matched controls. Prior history of autoimmune disease was a risk factor, and adrenal insufficiency may be a trigger. Patients with CD should be carefully monitored for autoimmune disease after remission.

The authors have no relevant relationships to disclose.

P8

Defining the Corticotroph Pituitary Neuroendocrine Tumor Microenvironment Using Spatial Single-Cell Transcriptome Imaging

Jayati Chakrabarti[1]; Saptarshi Mallick[1]; Kevin C.J. Yuen[2]; Andrew S. Little[3]; Yana Zavros[1]

[1]Department of Cellular and Molecular Medicine, University of Arizona College of Medicine, Tucson, Arizona, USA; Department of Neuroendocrinology, Barrow Neurological Institute, Phoenix, Arizona, USA[2]; Department of Neurosurgery, Barrow Neurological Institute, Phoenix, Arizona, USA[3]

Background: Cushing's disease (CD) is a debilitating disease caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary neuroendrocrine tumor (PitNET). The first-line treatment for CD is transsphenoidal surgery, which is followed by disease recurrence in 56% of patients. *Intra-PitNET cell heterogeneity, associated with a heterogeneous protein and the genomic landscape may lead to therapeutic failure, tumor adaptation and subsequently disease recurrence. However, the complexity of the PitNET microenvironment (ME) is remarkably understudied.* **Objective:** To define the cellular complexity of corticotroph subtype PitNET MEs at a spatial single-cell resolution to overcome the challenges of therapeutic failure and disease recurrence in CD patients. **Approach:** Single-cell RNA sequencing (scRNA-seq) was used to compare the transcriptomic profile and cell composition of CD patient PitNET tissue-generated organoids (PitNET^{org}) (**Mallick *et al.*, 2023, *Translational Res.***) to the patient's own tissue using the NanoString CosMx® Spatial Molecular Imager technology. **Results:** PitNET^{org} and PitNET tissues from the major morphological variants densely granulated, sparsely granulated and Crooke cell exhibited distinct PitNET ME. All the morphological variants exhibited the presence of cells co-expressing epithelial and stromal markers that was reflective of PitNETs undergoing epithelial-to-mesenchymal transition. Noteworthy, we identified differences in the cancer/tumor associated fibroblast (CAFs) phenotypes among the morphological variants. While inflammatory CAFs (iCAFs) were found infiltrating the Crooke cell PitNET ME. Hedgehog signaling and primary cilium-associated genes were expressed within the iCAFs. Myofibroblast CAFs (myCAFs) were predominantly found in sparsely and densely granulated tumors. A large macrophage infiltration was observed with the Crooke cell PitNET ME. **Conclusions:** Defining the complexity of the PitNET ME will provide fundamental insights in the pathogenesis of CD and potentially lead to the stratification of high-risk patients for disease recurrence. Reprogramming tumor-promoting signaling from CAFs is a potential therapeutic approach for the targeted therapy of PitNETs and prevention of disease recurrence.

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P9

Ectopic, CRH-Responsive Cushing's Syndrome, with Negative 68Ga-DOTA-TATE / 16 FDG PET/CT Imaging and Pituitary Microadenoma - Challenging Case Ended by Successful Outcome

Aleksandra Gilis-Januszewska[1, 2]; Anna Bogusławska[1, 2]; Ewelina Rzepka[1, 2]; Mari Minasyan[2]; Aleksandra Gamrat[2]; Alicja Hubalewska-Dydejczyk[1, 2]

[1]Jagiellonian University Medical College, Chair and Department of Endocrinology, Krakow, Poland; [2]Endocrinology, Oncologic Endocrinology and Nuclear Medicine Department, University Hospital in Krakow, Poland

ACTH dependent Cushing Syndrome (CS) is a rare disorder which often is a diagnostic and clinical challenge. We present a 57-year-old female patient with ectopic CS diagnosed in 2019. She presented severe clinical CS symptoms with hypokalemia (3,1 mmol/l). Elevated ACTH(408,4 pg/ml); cortisol in 24h urine collection(466,8 ug/24h); high nocturnal cortisol(15,7 ug/dl) were observed. CRH test done in 2019 showed rise of ACTH and cortisol (respectively 31% and 23%). There was no decline of cortisol level in 8 mg dexamethasone suppression test. Pituitary gland MRI, Computed Tomography of Abdomen and Thorax, colonoscopy, bronchoscopy, FDG PET-CT, 68GaDODATE PET/CT didn't identify the source of ACTH overproduction. In 2019 200 mg of Ketoconazole was introduced, followed by Osilodrostat (4 mg/daily) in February 2022. Multiple diagnostic procedures were repeated in 2022. CRH test showed cortisol rise by 31% and ACTH by 38%. In MRI a pituitary microadenoma (8x2.5x2.5mm) was found. However, BIPSS results were not suggestive for Cushing Disease. CT showed a calcification of pancreas and left lung lesion. 68GaDODATE PET/CT revealed a pathological expression of somatostatin receptors (SSR) in pancreas, but no pathological SSR expression in the left lung. Distal pancreatectomy was performed (06.2022). Histopathology revealed Intraductal Papillary Mucinous Neoplasms. After surgery patient presented persistent hypercortisolism. She was reconsulted by a multidisciplinary tumor board and wedge- peripheral resection of the left lung lower lobe was performed. Histopathology showed a typical carcinoid (NET G1, Ki67 2,5%). Currently, six month after the surgery the patient feels good on hydrocortisone supplementation. The diagnosis and the treatment of Ectopic Cushing syndrome often is challenging and might require long term observation and combination of multiple biochemical and radiological tools, which results may remain discrepant.

The authors have no relevant relationships to disclose.

P10

eGFR Cystatin is a More Accurate Indicator of Kidney Function Comparing to eGFR Creatinine in Patients with Mild Autonomous Cortisol Secretion

Leili Rahimi[1]; Jasmine Saini[1]; Elizabeth Atkinson[2]; Sara J Achenbach[2]; Andrea Kattah[3]; Irina Bancos[1]

[1]Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Department of Medicine, Mayo Clinic, Rochester, MN; [2]Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN; [3]Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN

Introduction: Patients with mild autonomous cortisol secretion (MACS) have higher prevalence of cardiovascular comorbidities including chronic kidney disease. However, considering that patients with MACS may have relative sarcopenia, it is unclear whether the creatine-based assessment of kidney function is accurate in this population.

Objective: To characterize the differences in assessing estimated glomerular filtration rate using cystatin (eGFRcys) versus creatinine (eGFRcre) in patients with MACS versus referent subjects.

Methods: Cross-sectional single-center study, 2019-2022. MACS was defined as serum cortisol concentration >1.8 mcg/dL after the 1 mg overnight dexamethasone suppression test (DST). For each patient, eGFRcre, eGFRcys and eGFRcre/eGFRcys ratio were measured and compared between the two groups. Body composition was measured by DXA scan. The Kruskal-Wallis test was used to compare measurements between groups.

Result: A total of 55 patients with MACS (median age 55 years (interquartile range, IQR 48-66), 39 (71%) women) and 76 referent subjects (median age 57 years (IQR 48-66), 52 (68%) women) were included.BMI was higher in patients with MACS (median 32.3 vs 30.2 kg/m^2 in referents, P=0.005). In the MACS cohort, the median cortisol following 1-mg DST was 3.2 ug/dL (IQR, 2.3-5.9). While assessment of kidney function with eGFRcre showed no differences between patients with MACS and referent subjects (median 82.1 vs 87.8 ml/min/1.73m^2, P=0.19), kidney function using eGFRcys was lower in MACS (median 78.0 vs 91.7 ml/min/1.73m^2 in referents, P<0.001), resulting also in a higher eGFRcre/eGFRcys ratio (median 1.08 vs 0.98 in MACS vs referents, P=0.008). After adjusting for age, sex, and BMI, higher eGFRcre/eGFRcys ratio was associated with lower lean mass (Spearman correlation of -0.19, P=0.030).

Conclusion: Creatinine-based eGFR assessment in patients with MACS underestimates the degree of kidney dysfunction, likely due to underlying mild sarcopenia. eGFRcys is a more accurate indicator of kidney function in patients with hypercortisolism.

The authors have no relevant relationships to disclose.

P11

Glucocorticoid Withdrawal Syndrome Following Surgical Cure for Endogenous Hypercortisolism: A Longitudinal Observational Study

Catherine D. Zhang[1,2]; Dingfeng Li[1,3]; Sumitabh Singh[1,4]; Malavika Suresh[1,5]; Karthik Thangamuthu[1]; Rohit Nathani[1,4]; Sara J. Achenbach[6]; Elizabeth J. Atkinson[6]; Jamie J. Van Gompel[7]; William F. Young, Jr.[1]; and Irina Bancos[1]

[1]Division of Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic, Rochester, Minnesota; [2]Division of Endocrinology and Molecular Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin; [3]Endocrine and Metabolism Institute, Cleveland Clinic, Cleveland, Ohio; [4]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; [5]Department of Internal Medicine, Medstar Health, Baltimore, Maryland; [6]Division of Clinical Trials and Biostatistics, Department of Quantitative Health Sciences, Mayo Clinic, Rochester, Minnesota; [7]Department of Neurosurgery, Mayo Clinic, Rochester, Minnesota

Background: Glucocorticoid withdrawal syndrome (GWS) is a scarcely studied phenomenon that complicates the recovery following surgical cure of hypercortisolism.

Objective: To characterize the presence and trajectory of glucocorticoid withdrawal symptoms in the postoperative period and to determine presurgical predictors of GWS severity.

Methods: In this single-center longitudinal observational study (8/2019 - 12/2021), glucocorticoid withdrawal symptoms were prospectively evaluated weekly for the first 12 weeks after surgical cure of hypercortisolism. Quality of life (CushingQoL and Short-Form-36 [SF-36]) and muscle function (hand grip strength, sit-to-stand test) were assessed at baseline and at 12 weeks after surgery. Study protocol was approved by the local Institutional Review Board.

Results: A total of 129 patients (mild autonomous cortisol secretion [MACS], *n* = 59 [46%]; adrenal Cushing syndrome [CS], *n* = 12 [9%]; pituitary CS, *n* = 51 [40%]; and ectopic CS, *n* = 7 [5%]) underwent curative surgery for hypercortisolism. Prevalent symptoms in the postoperative period were myalgias and arthralgias (50%), fatigue (45%), weakness (34%), sleep disturbance (29%), and mood changes (19%). Most symptoms persisted, while myalgias, arthralgias and weakness worsened during weeks 5-12 postoperatively. At 12 weeks after surgery, normative hand grip strength was weaker than at baseline (mean Z-score delta -0.37, *P*=0.009), while normative sit-to-stand test performance improved (mean Z-score delta 0.50, *P*=0.013). SF-36 physical component summary score worsened (mean delta -2.6, *P* =0.015), but CushingQOL score improved (mean delta 7.8, P<0.001) at 12 weeks compared to baseline. On multivariable analysis, presurgical CS disease severity was an independent predictor of GWS symptomology.

Conclusion: Glucocorticoid withdrawal symptoms were prevalent and persistent following surgical cure of hypercortisolism with presurgical CS disease severity predictive of postoperative GWS symptom burden. Differential changes observed in muscle function and quality of life in the early postoperative period may reflect the competing influences of GWS and recovery from hypercortisolism.

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Glucose Metabolism in Skeletal Muscle and Adipose Tissue in Patients with Cushing Syndrome-Assessment with the Use of 2-[18F]FDG PET- a Pilot Study

E. Rzepka[1*]; J. Kokoszka[2*]; M. Opalinska[1]; K. Sitarz[3]; A. Grochowska[4]; A. Sowa-Staszczak[1]; A. Hubalewska-Dydejczyk[1]; A. Gilis-Januszewska[1]

[1]Jagiellonian University Medical College, Chair and Department of Endocrinology, Krakow, Poland; [2]Endocrinology, Oncologic Endocrinology and Nuclear Medicine Department, University Hospital in Krakow, POLAND; [3]University Hospital in Krakow, Poland; [4]Department of Radiology, University Hospital in Krakow, Poland
**first co-authorship of equal rank*

In patients with Cushing's syndrome (CS) the worsening of muscle quality is one of the metabolic consequences of hypercortisolemia. Muscle steatosis and myopathy are some of known mechanism, however relationship to inflammation and glucose metabolism is not well investigated.

The aim of our study was to assess glucose metabolism with the use of 2-[18F]FDG PET/CT in skeletal muscle and adipose tissue in patients with ectopic ACTH-syndrome. Analysis of 2-[18F]FDG PET/CT scans in 12 patients with ectopic Cushing syndrome (ECS) in comparison to age and sex-matched control group was performed. On unenhanced CT scans the body composition on cross-sectional computed tomography images at the L3 level - skeletal muscle area (SMA), skeletal muscle index (SMI), visceral fat area (VFA), visceral fat index (VFI), subcutaneous fat area (SFA), subcutaneous fat index (SFI), intermuscular adipose tissue (IMAT), bone density in vertebrae L3 was assessed.

Psoas muscle (at the L3 vertebra) and femoris muscle (medial vastus of the quadriceps femoris muscle at the mid-thigh level) metabolic

volume (MV), SUV peak, lesion glycolysis (LG) in both right and left muscle groups were evaluated based on the 2-[18F]FDG-PET scan results. The results were related to the hormonal status: ACTH, midnight cortisol, cortisol after 1mg of dexamethasone.

The comparison of glucose metabolism muscle and fat composition assessed by 2-[18F]FDG-PET and CT respectively, showed inverse correlation between SMI and metabolic volume of femoris muscle (p=0.044). Moreover, ACTH concentration was negatively correlated with metabolic volume and SUV peak of psoas muscle (p=0.044 and p=0.033, respectively).

Lower SMI with increased 2-[18F]FDG activity in femoris muscles may indicate increased inflammatory status in intramuscular adipocytes and fibrotic tissue. Negative correlation between ACTH and glucose metabolism in psoas muscle may potentially reflect better muscle health in patients with lower exposure to metabolic impairment associated with Cushing's syndrome.

The authors have no relevant relationships to disclose.

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Hydrocortisone vs Prednisone During Recovery Following Surgical Cure for Endogenous Hypercortisolism: A Longitudinal Observational Study

Sandooja R[1], Gregg- Garcia R[1], Zhang CD[2], Achenbach S[4], Atkinson E[3], Van Gompel J[4], Young WF[1], Bancos I[1]

[1]Division of Endocrinology, Mayo Clinic, Rochester, MN; [2]Division of Endocrinology, Medical College of Wisconsin; [3]Division of Clinical Trials and Biostatistics, Mayo Clinic, Rochester, MN; [4]Department of Neurological Surgery, Mayo Clinic

INTRODUCTION: Glucocorticoid withdrawal syndrome (GWS) is a constellation of symptoms that occurs after successful surgery for endogenous hypercortisolism. The objective of this study is to compare hydrocortisone versus prednisone for GWS symptoms.

METHODS: Study design: Single-center prospective longitudinal observational study, 2019-2023.

Participants: Adults with Cushing syndrome (CS) and mild autonomous cortisol secretion (MACS) with post-operative adrenal insufficiency and treated with hydrocortisone or prednisone.

Measurements: Clinical and biochemical severity scores were calculated. Quality of life(QOL) was assessed using Short Form-36 (SF-36) and Cushing QOL, and GWS was assessed using weekly AddiQOL surveys.

RESULTS: Of 121 patients, 91 patients were treated with hydrocortisone and 30 with prednisone. No differences in age (median age 51 vs 54 years, *P*=0.48), sex (84 vs 90% women, *P*=0.387), etiology of hypercortisolism (ACTH-dependent: 44% vs 43%, *P*=0.280), clinical severity (median score 13 vs 11, *P*=0.5327), or biochemical severity (median score of 6 vs 5, *P*=0.559) were noted between groups.

When assessed at 4-, 8-, and 12-weeks post-surgery, the prevalence and trajectory of symptoms (fatigue, myalgias/arthralgias, sleep, headaches, nausea, weakness, mood) was similar in patients treated with hydrocortisone and prednisone (P>0.05 for all).

When compared to baseline, the overall Cushing QOL score 12 weeks post-surgery improved in both groups (mean delta 8.9 vs 9.0 , P=0.772). No differences in the hydrocortisone vs prednisone treatment were found in the SF-36 physical component score (mean delta of -1.7 vs -0.5 , P=0.416) and SF-36 mental component score (mean delta 2.3 vs 2.9 , P=0.652).

On multivariable analysis, age (est 0.198, P= 0.016), clinical severity score (est-0.715, P= 0.002), but not glucocorticoid type (est-0.850, P=0.728) were associated with GWS symptom burden.

CONCLUSION: Choosing hydrocortisone versus prednisone after curative surgery for hypercortisolism did not impact the severity or trajectory of GWS. Baseline clinical severity assessment was associated with the GWS burden.

The authors have no relevant relationships to disclose.

P14

Improvement in Fibrinolysis Parameters in Patients with Cushing's Syndrome after Surgery – A Case Series

Francisco J. Guarda[1,2], David Rodríguez[3,4], Thomas Uslar[1,5], René Baudrand[1,5], Maite Domenech[6], Pablo Villanueva[2,7], Flavia Nilo[1,2]

[1]Endocrinology Department and Center for Translational Endocrinology (CETREN), Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile; [2]Pituitary Tumor and Skull Base Endonasal Endoscopy Program, Red de Salud UC-CHRISTUS, Santiago, Chile; [3]Clinical Laboratory Department, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile; [4]Thrombosis and haemostasis laboratory, Clinical Laboratories Service, Red de Salud UC-CHRISTUS, Santiago, Chile; [5]Adrenal Tumor Program, Red de Salud UC-CHRISTUS, Santiago, Chile; [6]School of Medicine, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile; [7]Neurosurgery Department, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

INTRODUCTION: Hypercortisolism is associated with a prothrombotic state in which fibrinolysis is impaired. There is scant agreement on how to evaluate fibrinolysis; thus, it is rarely performed clinically. Furthermore, its response to adrenal or pituitary surgery has not been addressed.

OBJECTIVE: To describe the variation in fibrinolysis parameters, measured with a validated clot lysis-time assay (CLTA) in platelet-free plasma (PFP) in adrenal or pituitary hypercortisolism, before and after surgical resolution of cortisol excess.

METHODS: CLTA was performed in two patients with confirmed hypercortisolism before and 24 hours after surgery. Pilot study. RESULTS: **Case 1:** a 25-year-old female presented with weight gain. Physical examination: mild red striae and central adiposity. Lab results: dexamethasone suppression test (DST) 10.3µg/dL (Reference interval [RI]<1.8µg/dL), free urine cortisol (UFSC) 168µg/g creatinine (RI<106), late-night salivary cortisol 0.2 and 0.13µg/dL (RI<0.1), and ACTH 5pg/mL (RI:10-60). Abdomen computed tomography: 8cm left adrenal mass. Elevated CLTA was obtained prior to surgery (1834 seconds, RI:467-1478). Adrenalectomy was performed, which was compatible with adrenal carcinoma. She developed significant improvement of hypercortisolism-associated symptoms and low-dose hydrocortisone was initiated. CLTA performed 24 hours after surgery: 891 seconds. **Case 2:** a 34-year-old man presented with evident Cushing´s syndrome features. Lab work: DST 14.5µg/dL, UFC 380µg/g, and ACTH 45pg/mL. Sellar MRI: no pituitary lesion. BIPSS: central origin. CLTA prior to surgery: very prolonged (2234 seconds). TSS: pituitary adenoma. He developed corticotropic insufficiency and hydrocortisone was initiated. Early postop CLTA showed significant reduction (1505 seconds).

CONCLUSION: This case series shows that CLTA improved significantly after early surgical resolution in both patients. If confirmed in large cohorts, CLTA may aid in the evaluation of thrombotic risk in Cushing's syndrome and, theoretically, predict who may benefit from postoperative antithrombotic prophylaxis.

The authors have no relevant relationships to disclose.

P15

Incidence of and Risk Factors for Postoperative Venous Thromboembolism in Cushing's Disease

Masaaki Mikamoto[1], Hang Lee[2], Lisa B. Nachtigall[3], Brooke Swearingen[1], Karen K. Miller[3], Pamela S. Jones[1]

[1]Department of Neurosurgery, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA; [2]Massachusetts General Hospital Biostatistics Center, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA; [3]Neuroendocrine Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Objective: To investigate the incidence of and risk factors for postoperative venous thromboembolism (VTE) in patients who have undergone transsphenoidal surgery (TSS) for Cushing's disease (CD).

Methods: 315 patients with CD and 559 patients with non-functioning pituitary adenomas (NFPAs) were studied. We compared: 1) the incidence of symptomatic VTE between CD and NFPAs occurring up to 90 days post-TSS, and 2) risk factors among patients with CD with and without VTE. Continuous variables were compared using the Mann-Whitney U test and are reported as median (interquartile range). Fisher's exact test was used to compare proportions. A two-tailed p-value < 0.05 was considered statistically significant.

Results: Five of 6 patients with CD with symptomatic post-TSS VTE experienced them within the first week after surgery ("early"), while no patients with NFPA had early VTE (p=0.006). Two of these patients presented with symptomatic pulmonary embolism (PE) on postoperative day (POD) 1 or 2. Two of 3 patients who developed early deep venous thrombosis (DVT) had a history of previous DVT. In contrast, the overall incidence of post-TSS VTE within 90 days post-TSS was similar between CD and NFPAs [6/315(1.9%) versus 4/559(0.7%), p=0.18]. All patients in both groups diagnosed with VTE >1 week post-TSS had additional risk factors: high-dose steroid administration POD 1 (patient with NFPA), additional surgery, prior DVT, or prolonged inpatient stay. CD remission status was not a predictor of post-TSS VTE. Patients who were discharged on POD 1 trended toward a lower incidence of post-TSS VTE compared with longer stays (0.9% versus 4.4%, p=0.06).

Conclusion: Patients with CD may have a higher risk of VTE, including symptomatic PE, in the immediate post-TSS setting. Additional data are needed to characterize the risk factors for early VTE and identify those patients who may benefit from perioperative prophylaxis.

The authors have no relevant relationships to disclose.

P16

In Patients with Cushing Disease and a Visible Tumor on MRI, BIPSS Does Not Add to the Accuracy of Predicting Tumor Lateralization

Michelle D. Lundholm[1], Kevin M. Pantalone[1], Pratibha Rao[1], Amir H. Hamrahian[2] and Divya Yogi-Morren[1]

[1]Cleveland Clinic Endocrinology & Metabolism Institute, Cleveland, OH, USA; [2]Johns Hopkins Department of Endocrinology, Diabetes and Metabolism, Baltimore, MD, USA

Introduction: There is controversy surrounding the value of bilateral inferior petrosal sinus sampling (BIPSS) for lateralization in Cushing Disease (CD) when there is a visible pituitary lesion on pre-operative imaging. This study compares lateralization results between BIPSS and pituitary MRI against surgical localization.

Methods: A single-center retrospective chart review was conducted on patients with pathology-confirmed CD between 2003-2018, with unilateral pituitary tumor visible on MRI and successful pre-operative BIPSS. Bilateral sellar exploration was performed surgically in all cases regardless of BIPSS or MRI lateralization results. Descriptive statistics were used.

Results: Of 27 patients included, all had BIPSS results consistent with CD and all lateralized. The median age at diagnosis was 42 years (range 21-69 years) and 85% were female (N=23). The median tumor size on MRI was 5 mm (range 3-8 mm). Prolactin adjustment was performed in the interpretation of BIPSS in 26 cases (96%). MRI correctly lateralized 26 tumors (96%), whereas BIPSS correctly lateralized 23 tumors (85%). Of the 5 cases where MRI and BIPSS disagreed on laterality, the operative report was consistent with MRI lateralization in 3 cases, and midline disease in the remaining 2 cases. There were no cases where BIPSS lateralization was correct when MRI lateralization was incorrect. In the subset of 13 patients with tumors measuring <6 mm on MRI, MRI imaging lateralization was correct in all 13 (100%) cases and BIPSS lateralization was correct in 11 (85%). There were no serious complications from BIPSS, though 4 patients (15%) experienced a minor adverse event (headache, hematoma).

Conclusion: Overall, when a tumor is visible on MRI (≥3 mm), BIPSS does not add to the accuracy of determining tumor lateralization.

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P17

Significant Variability in Postoperative Thromboprophylaxis in Cushing's Disease Patients: A Survey of the North American Skull Base Society and the AANS/CNS Joint Tumor Section

Alexandra J. White[1,2], João Paulo Almeida[2,3], Jordan C. Petitt[4], Divya Yogi-Morren[5], Pablo F. Recinos[1,2], Varun R. Kshettry[1,2]

[1]Department of Neurological Surgery, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA; [2]Section of Skull Base Surgery, Rose Ella Burkhardt Brain Tumor & Neuro-oncology Center, Neurological Institute, Cleveland Clinic, Cleveland, OH; [3]Department of Neurosurgery, Mayo Clinic, Jacksonville, FL, USA; [4]Case Western Reserve University School of Medicine, Cleveland, OH, USA; [5]Department of Endocrinology, Diabetes & Metabolism, Cleveland Clinic Foundation, Cleveland, OH, USA

Introduction: Cushing's disease (CD) is associated with hypercoagulability and an increased risk of perioperative venous thromboembolic events (VTEs). This risk persists for some time even after successful transsphenoidal surgery (TSS). There are no current guidelines for pharmacologic thromboprophylaxis in this patient population.

Objective: Characterize existing thromboprophylaxis management practices in patients undergoing TSS for CD.

Methods: An anonymous Ethics Committee-approved RedCap survey comprised of questions about perioperative thromboprophylaxis in CD patients was distributed via the AANS/CNS Joint Tumor Section and the North American Skull Base Society (NASBS) email lists.

Results: The survey was distributed to 554 attending neurosurgeons who are members of the AANS/CNS Joint Tumor Section and 1,094 members of NASBS, asking that members who surgically treat Cushing's Disease respond. 60 responses (3.0%) were received. 52 (87.6%) respondents are involved in the postoperative management of CD patients. Eleven (21.2%) of respondents perform radiographic screening (e.g. leg ultrasound) for VTE in at least some patients preoperatively, while 18 (34.1%) screen at least some patients postoperatively (p = 0.14). 36 (69.2%) treat all patients with postoperative chemoprophylaxis, 8 (15.4%) treat some patients, while 8 (15.4%) do not use chemoprophylaxis. Preferred chemoprophylaxis varies as 26 (59.1%) administer low molecular weight heparin, 14 (31.8%) give unfractionated heparin, 1 (2.3%) give direct oral anticoagulants, and 3 (6.8%) give aspirin. The majority (28, 53.8%) of respondents perceive the VTE risk in this patient population to be 0-5%, 16 (30.8%) perceive the risk to be 6-10%, and 8 (15.4%) perceive it to be 11-20%.

Conclusions: Although hypercoagulability is a known phenomenon, there is still great variability in VTE detection and postoperative prevention practice patterns in CD patients. This study highlights the need for increased awareness about this potential complication and the need for prospective studies to clarify optimal pharmacologic chemoprophylaxis strategies and duration in this patient population.

The authors have no relevant relationships to disclose.

P18

The OPTICS Study: Study Design and Baseline Characteristics of a Long-Term, Open-Label Study of Levoketoconazole for the Treatment of Cushing's Syndrome

Fred Cohen,[1] Robbie Huang,[2] Dawn Harper[2]

[1]Independent Consultant, Washington Crossing, PA, USA; [2]Xeris Pharmaceuticals, Inc., Chicago, IL, USA

Objective: The open-label extension OPTICS study was designed to assess long-term safety and efficacy durability of levoketoconazole in endogenous Cushing's Syndrome (CS).

Methods: All sites obtained EC approval and written informed consent prior to enrolling a subject into OPTICS. Subjects who had participated in the SONICS or LOGICS Phase 3 studies were generally eligible to enroll. Those who had previously discontinued levoketoconazole due to safety, tolerability, or lack of efficacy were ineligible. Subjects that completed a parent study were to use their prior established dose (150 to 1200 mg/day) initially, with modifications permitted for safety or loss of efficacy following titration. Twelve subjects were enrolled prior to completing dose titration in LOGICS; they completed titration in OPTICS using LOGICS titration criteria. Follow-up visits occurred approximately every 3 months, with mean urinary free cortisol (mUFC) measured at least every 6 months, continued for up to 3 years. Exploratory efficacy endpoints included changes in mUFC and late-night salivary cortisol; clinical signs and symptoms of CS; and CS comorbidity biomarkers. Safety was assessed by adverse events, physical examination, laboratory evaluations, electrocardiography, and annual pituitary MRI (with history of tumor).

Results: Of 166 unique subjects enrolled in 1 or both parent studies, 52 at 28 sites in 11 countries in the USA and Europe were screened for OPTICS and 51 enrolled. Mean (SD) age was 44.1 (11.2) years, 78.4% female, and 90% White. Mean BMI was 29.6 (7.1) and 31.4% had diabetes. Most (86%) subjects had Cushing's Disease with a mean (SD) 89.3 (73.9) months since diagnosis; 77% had received therapy for CS prior to use of levoketoconazole.

Conclusion: The population enrolled in OPTICS resembles the parent studies. OPTICS will soon provide long-term data to inform chronic treatment of CS with levoketoconazole.

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GENETICS

P19

Generation of Isogenic and Homozygous MEN1 Mutant Cell Lines from Patient-Derived iPSCs Using CRISPR/Cas9

Derya Metin-Armagan[#1], Naomi Even-Zohar[#1], Anat Ben-Shlomo[1], Dhruv Sareen[2], Shlomo Melmed[1]

[1]Pituitary Center, Dept of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [2]iPSC Core, David and Janet Polak Foundation Stem Cell Core Laboratory, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [#]Contributed Equally

MEN1, an autosomal dominant disorder caused by mutations in the tumor suppressor gene MEN, manifests with co-occurrence of multiple endocrine/neuroendocrine neoplasms. An induced pluripotent stem cell (IPSC) line derived from an index patient (CS011iMEN1.n4, produced in the Cedars-Sinai iPSC Core facility) carrying the mutation c.1273C>T (p.Arg465*) was edited using a single multiplex CRISPR/Cas approach to create an isogenic control non-mutated line (CS011iMEN1.n4-ISOF1) and a homozygous double mutant line (CS011iMEN1.n4-HOMO5). All three cell lines showed typical pluripotent cell morphology on Brightfield microscopy and positive immunostaining for pluripotency markers SSEA4, SOX2, OCT4, TRA-1-60, TRA-1-81, and NANOG. PCR amplification of a 627 bp sequence spanning the edited site and Sanger sequencing verified the correct editing. STR profile and interspecies contamination testing was analyzed and comparative analysis conducted. All three cell lines exhibited a normal karyotype with no clonal abnormalities. On subsequent culturing, we observed faithful embryoid-body formation and the ability to differentiate to all three germ layers. All clones were proven mycoplasma-free. Conclusions: These cell lines will be useful for elucidating subcellular pathways subserving MEN1 syndrome pathophysiology and for identifying targets to facilitate screening for potential MEN1 therapeutic molecules.

The authors have no relevant relationships to disclose.

P20

The Genetic Background of Acromegaly in a Tertiary Referral Centre in Krakow, Poland

Anna Bogusławska[1]; Magdalena Godlewska[1]; Ewelina Rzepka[1]; Marta Korbonits[2]; Alicja Hubalewska-Dydejczyk[1]; Aleksandra Gilis-Januszewska[1]

[1]Chair and Department of Endocrinology, Jagiellonian University, Medical College, Cracow, Poland; [2]Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London

Introduction: Acromegaly is the most genetically determined pituitary disease.

Objectives: We studied the prevalence of syndromic disease and germline mutations (*AIP, MEN1, GNAS, PRKAR1A, CDKN1b)* in a cohort of unselected, consecutive patients with acromegaly.

Materials and methods: A total of 133 patients (79 females, 54 males, age range 16-75 years) with somatotroph pituitary neuroendocrine tumor who were studied at the Jagiellonian University (Krakow), a tertiary referral center, between 2019-2022, were enrolled in this study. *AIP* testing was performed in all patients with acromegaly, whereas other genes were tested in young patients (<30 years-old), patients with macroadenoma or with syndromic features. Sanger sequencing was used for the assessment of *AIP, MEN1*, *GNAS, PRKAR1A, CDKN1B* gene variants, and multiplex ligation-dependent probe amplification (MLPA) was used for the assessment of *PRKAR1A* negative results in Sanger sequencing.

Results: Overall, a total of 12.2% (16/131) patients presented clinical manifestations of syndromic disease or gene variants which might be associated with acromegaly.

AI*P* variants were identified in 7.7% (8/104), *MEN1* alterations were detected in 3.6% (3/84), McCune-Albright syndrome was clinically diagnosed in one patient (0.75%), one patient was clinically diagnosed with Carney complex (0.75%), and three patients presented MEN1 associated symptoms (acromegaly and hyperparathyroidism) with negative genetic evaluation for *MEN1* and *CDKN1B* (Sanger sequencing). One patient presented Neurofibromatosis type 1 features, two additional patients presented some of Carney complex symptoms. None of patients harbored *PRKAR1A* and *CDKN1B* variants. Further confirmatory genetic analysis are planned in patients with clinical suspicion of syndromic disease and negative Sanger and MLPA testing.

Conclusions: This study is one of the first to show genetic abnormalities among adult patients with acromegaly in Poland. Genetic testing in acromegaly should be considered to personalize and optimize the treatment of patients.

The authors have no relevant relationships to disclose.

P21

Late Diagnosis of McCune Albright with Severe Kyphoscoliosis, Acromegaly and Tertiary Hyperparathyroidism

Anna Bogusławska[1], Marta Korbonits[2], Alicja Hubalewska-Dydejczyk[1], Aleksandra Gilis-Januszewska[1]

[1]Chair and Department of Endocrinology, Jagiellonian University, Medical College, Cracow, Poland; [2]Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London

McCune–Albright syndrome (MAS) is caused by somatic activating variants of GNAS gene. Due to the mosaic state of variants, the clinical presentation of MAS widely varies. Biological samples bearing a low level of mosaicism frequently lead to false-negative results with an underestimation of causative molecular alterations. Here, we present the case of a 47-year-old woman with acromegaly, subclinical hyperthyroidism, hypercalcemia, café-au-lait spots and severe kyphoscoliosis. Our patient was originally admitted to the Pulmonary Unit due to progressive pulmonary insufficiency secondary to severe scoliosis. Radiographic imaging revealed osteolytic lesions of the axial skeleton- suspected to be metastatic. Upon physical examination, hyperpigmented skin lesions on the neck, features of acromegaly, and severe scoliosis were noted. 18F-fluorodeoxyglucose positron emission tomography did not confirm metastases; however, a pituitary lesion was revealed. The laboratory workup confirmed acromegaly. Additionally, mild hypercalcemia, normophosphatemia with elevated parathyroid hormone level, and decreased urine calcium excretion were found. Further examinations revealed kidney stones, cholecystolithiasis, and severe osteoporosis. In clinical follow-up visits, hypophosphatemia has been observed. Bone scintigraphy revealed increased tracer uptake in the axial skeletal system, shoulders, sternoclavicular joints, and hips; Biochemical analysis revealed subclinical hyperthyroidism. Genetic testing was negative for MEN1 and CDKN1B (Sanger sequencing) but revealed a common germline GNAS variant NM_000516.7:c.531-13_531-10del (rs576071932)–classified as a variant of uncertain significance (RCV000597562.1) with minor allele frequency of 0.265%. Further genetic evaluation of pituitary tissue was negative for the *GNAS* mutation (Sanger sequencing), however blood sample is now verifying in Digital Droplet Polymerase Chain Reaction. Acromegaly, skeletal deformity, hyperpigmented skin lesions, and hyperfunction of the thyroid and parathyroid glands may lead to a suspicion for MAS. The diagnosis of MAS is often made clinically, based on 2 or more characteristic symptoms, while the phenotype depends on the affected tissues. Genetic confirmation of this rare syndrome can be challenging.

The authors have no relevant relationships to disclose.

GROWTH HORMONE/ACROMEGALY

P22

Adherence and Persistence of Somatostatin Receptor Ligands in Acromegaly and Neuroendocrine Tumors: A Systematic Review

Richard A. Feelders[1], Aude Houchard[2], Christelle Pommie[2], Julianna Catania[3], Anna Bobrowska[4], Antonio Ribeiro-Oliveira Jr.[5]

Erasmus University Medical Center, Rotterdam, The Netherland[1], Ipsen, Boulogne Billancourt, France[2], Costello Medical, Boston, MA, USA[3], Costello Medical, Cambridge, UK[4], Ipsen, Cambridge, MA, USA[5]

Background: Adherence and persistence of somatostatin receptor ligands (SRLs) are important to avoid uncontrolled disease (acromegaly) and progression (neuroendocrine tumors [NETs]). We conducted a systematic review assessing adherence, persistence and treatment duration (TD) of SRLs in acromegaly and NETs.

Methods: MEDLINE, Embase, and the Cochrane Library were searched in October 2022. Studies reporting adherence or persistence of SRLs in adults with acromegaly or NETs were included.

Results: Nineteen studies reported on acromegaly, 21 on NETs, and one on both. TD was the most frequently reported outcome for first-generation SRLs (fg-SRLs) in observational studies (n=27). Mean/median TD in acromegaly studies ranged from 12.0–112.8 months (n=11); in three studies ≥50.0% of patients had previous surgery and/or radiotherapy. Mean/median TD in NETs ranged from 10.0–154.0 months (gastroenteropancreatic NETs [n=6; 16.0–154.0 months], lung NETs, [n=4; 10.0–43.3 months], and other mixed NETs studies, [n=6; 10.0–40.8 months]). The proportion of patients adhering to fg-SRLs (taking 80%–100% of prescribed doses) was 74.0%–94.5% in acromegaly (n=3) and 76.0%–85.8% in NET studies (n=2). There was a literature gap for reporting persistence (n=4). One study reported mean persistence (the first occurrence of a patient more than 15 days overdue for injection) of 12.5–16.6 months for patients with acromegaly; three studies reported 44.4%–93.0% of patients with NETs were persistent. Data were not stratified by previous surgery, radiotherapy, or carcinoid syndrome, precluding analysis of their impact on adherence and persistence. Heterogeneity in adherence and persistence definitions and study design precluded meta-analyses.

Conclusions: Although SRL treatment in acromegaly is lifelong for responders, TD range was similar in both indications, likely due to variations in TD reporting and follow-up length. SRL treatment adherence appeared high in acromegaly and NETs; fg-SRL persistence is not well studied for either disease.

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P23

Adherence to Medication and Healthcare Resource Use in Acromegaly: An Analysis of Real-World Insurance Claims Data

Maria Fleseriu[1], Ariel Barkan[2], Thierry Brue[3], Edouard Duquesne[4], Aude Houchard[4], Maria del Pilar Schneider[5], Antonio Ribeiro-Oliveira Jr.[6], Shlomo Melmed[7]

[1]Pituitary Center Oregon Health and Science University, Portland, OR, US; [2]A. Alfred Taubman Health Care Center, University of Michigan, Ann Arbor, , MI, US; [3]Aix-Marseille University, Marseille, France; [4]Ipsen, Boulogne Billancourt, France; [5]Ipsen, Les Ulis, France; [6]Ipsen, Cambridge, US; [7]Cedars-Sinai Medical Center, Los Angeles, CA, US

Background: Although medical treatments for acromegaly are well-established, real world evidence (RWE) on medication adherence and healthcare resource utilization (HCRU) is limited. We evaluated adherence, comorbidities, and HCRU among United States patients treated with somatostatin receptor ligands (SRLs), growth hormone receptor antagonists (GHRAs), or dopamine agonists (DAs).

Methods: De-identified data were extracted from MarketScan® (1/1/2010–7/31/2022). Eligibility: monotherapy/combination therapy (≥2 treatments overlapping for >3 months) for ≥90 days without treatment gaps; ≥2 acromegaly-associated claims; data ≥3 months before/≥6 months after diagnosis/first treatment claim (earlier); ≥18-years-old at diagnosis. First-line treatment outcomes: adherence (proportion of days covered [PDC] by prescription; mean [95% confidence interval]). Among patients receiving SRLs (lanreotide depot [LAN], octreotide long-acting release [OCT]) monotherapies: extended dosing interval (EDI) use. Among the full cohort, during first year post diagnosis: comorbidities (% cohort); HCRU (outpatient visits; mean [95% confidence interval] events).

Results: Of 882 patients, female: 50.1%; mean age at diagnosis: 48.6 years (standard deviation 13.6 years); median follow-up: 2.7 years. Adherence (PDC, first-line): 0.67 (0.60–0.70; DAs); 0.77 (0.75–0.79; LAN); 0.74 (0.72–0.76; OCT); 0.75 (0.71–0.78; GHRAs). Among patients receiving SRLs, 22/189 (LAN) and 9/250 (OCT) had EDIs. Most prevalent comorbidities: cardiovascular disorders (46.3%); hypopituitarism (17.6%); malignant neoplastic disease (16.7%). Most (99.8%) had ≥1 outpatient service; 34.6% had ≥1 inpatient

admission; 28.3% had ≥1 emergency room visit. Mean outpatient visits: 16.1 (15.07–17.28), 21.0 (19.68–22.53), and 29.1 (27.10–31.22) among patients with no comorbidities (35.7%), 1 comorbidity (41.2%), and ≥2 comorbidities (23.1%), respectively.

Conclusions: Adherence to medication for acromegaly, an important factor in long-term outcomes, was lowest for DAs (oral treatment), compared to SRLs, although biochemical data were unavailable. Significantly increased outpatient visits among patients with more comorbidities highlight comorbidity-related disease burden. RWE can provide healthcare professionals with insights on treatment adherence for different medication classes to optimize patient outcomes.

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P24

Association Between Nonalcoholic Fatty Liver Disease and Growth Hormone Deficiency in Patients with Nonfunctioning Pituitary Adenoma

Yoon-a Hwang; Youngsook Kim; Eun-Jig Lee; Cheol Ryong Ku

Yonsei University College of Medicine, Seoul, Korea, Republic of

Objective: We investigated the association between nonalcoholic fatty liver disease (NAFLD) and growth hormone deficiency (GHD) in patients with non-functioning pituitary adenoma (NFPA).

Methods: Patients with NFPA who underwent transsphenoidal adenectomy between January 2005 and December 2018 were recruited. Pituitary function was determined by the insulin tolerance test, thyroid hormone assay, and gonadal hormone levels. NAFLD was defined as a hepatic steatosis index greater than 36.

Results: 278 patients were included for the analysis. Mean age was 44.2 years and 58.6%[n=163] patients were female. Among 278 patients,103 (37.0%) had GHD, 139 (50.0%) had hypogonadism. 75 out of 278 patients (27.0%) had NAFLD. The prevalence of NAFLD was significantly higher in patients with GHD than in those without (36.9% vs. 21.1%, p=0.01). Even after adjusting for age, total cholesterol level, gonadal function, and prolactin level, patients with GHD had approximately two-fold higher prevalence of NALFD than those without GHD (adjusted odds ratio [OR]=1.85, 95% confidence interval [CI]=1.05-3.28, p=0.03). Among female patients, the prevalence of NALFD was significantly higher in those with GHD than in those without (adjusted OR=2.39, 95% CI=1.03-5.55, p=0.04). On the other hand, the prevalence of NAFLD among male patients was statistically similar between patients with and without GHD (p>0.05). In addition, gonadal function did not affect the prevalence of NAFLD in patients with NFPA (29.3% with eugonadism vs. 47.8% with hypogonadism, p=0.14).

Conclusion: The prevalence of NAFLD among patients with NFPA was twice as high as among patients without GHD. Thus, screening for NAFLD may be necessary in NFPA patients with GHD.

The authors have no relevant relationships to disclose.

P25

CD68+ and CD8+ Immune Cells are Associated to the Growth Pattern of Somatotroph Tumors and to the Response to First Generation Somatostatin Analogues

Sabrina Chiloiro[1-2], Antonella Giampietro[1-2], Marco Gessi[3], Liverana Lauretti[4-5], Pier Paolo Mattogno[4-5], Lorenzo Cerroni[1], Angela Carlino[3], Quintino Giorgio De Alessandris[4-5], Alessandro Olivi[4-5], Guido Rindi[3], Alfredo Pontecorvi [1-2], Laura De Marinis[1-2], Francesco Doglietto[4-5], Antonio Bianchi [1-2]

[1]UOC Endocrinology and Diabetology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy; [2]Department of Translational Medicine and Surgery, Università Cattolica del Sacro Cuore, Roma, Italy; [3]Department of Woman and Child Health Sciences and Public Health, Anatomic Pathology Unit, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Roma, Italy; [4]Neurosurgery Unit, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy

Introduction: Somatotropinomas are pituitary tumors, with a heterogenous clinical behavior. The tumor microenvironment regulates the interaction between tumor cells and the host immune system, potentially modulating the tumor behavior. We aim to investigate the tumor immune infiltration in a cohort of medically naïve acromegaly patients.

Material and methods: A retrospective, monocenter study was designed to analyze the presence of CD3+, CD20+, CD138+, CD4+, CD8+, CD68+ immune cells in samples of somatotropinomas and their prognostic significance on tumor behavior and response to first generation somatostatin analogues (fg-SSA).

Results: Thirty-six patients (23 females) entered the study. Macro-adenomas were identified in 23 cases: 12 with cavernous sinus invasion. The number of CD8+ lymphocytes positively correlated with CD4+ lymphocytes (p=0.05, r:0.245) and with CD68+ macrophages (p=0.01, r=0.291). The CD8+/CD4+ ratio inversely correlated with CD68+/CD8+ ratio (p<0.001, r=-0.626). CD68+ macrophages positively correlated with tumor size (maximum diameter p=0.003, r=0.574; volume p=0.009, r=0.566) and were more numerous in somatotropinomas with Ki-67>3% (median 65/HPF, IQR:15), compared to cases with Ki67<3% (median 50/HPF, IQR:22, p<0.001). CD8+ and CD138+ lymphocytes were more numerous in cases responsive to fg-SSA (respectively median 18/HPF IQR:18 and median 8/HPF IQR: 6.5) as compared to fg-SSA not-responsive cases (median 14.5/HPF IQR:40 p=0.03; median 3.5/HPF IQR: 14 p=0.03). CD8+ lymphocytes acts as single predictor of response to fg-SSA, independently from age, GH and IGF-I levels, tumor dimension and invasion.

Conclusion: Our results support that in somatotropinomas, lymphocytes and macrophages generate an immune network and the characteristic of the immune infiltrate may predict treatment outcome.

The authors have no relevant relationships to disclose.

P26

Clinico-Radiological and Pathological Predictors of Outcome in Patients with Acromegaly Following Transsphenoidal Surgery

Sanish Ancil[1]; Liza Das[1,2]; Subin S[1]; Chirag Kamal Ahuja[3]; Sivashanmugam Dhandapani[4]; Rajesh Chhabra[4]; Kirti Gupta[5]; Pinaki Dutta[1]

Departments of [1]Endocrinology, [2]Telemedicine, [3]Radiodiagnosis, [4]Neurosurgery, [5]Histopathology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

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Background: Acromegaly is primarily treated by transsphenoidal surgery (TSS), but has a remission rate varying from 30 to 85 %. Determinants of remission in acromegaly following TSS may help in personalized management of patients with residual disease.

Materials and methods: This was a monocentric ambispective study in acromegaly patients post TSS with an aim to study the predictors of outcome. Clinical profile, radiological parameters (tumour size, Knosp grading and T2 signal-intensity) and pathological variables (SSTR2 and SSTR5 positivity, Ki67 index and CAM5.2) were recorded. These were correlated with biochemical remission at 3 months post TSS as well as the response to adjuvant somatostatin analogues (SSA) therapy.

Results: There were a total of 61 patients in the study with mean age at diagnosis being 38.5 ± 12.0 years, female preponderance (67.2%) and frequent presence of macroadenomas (90.2%). The clinico-radiologic predictors of remission were age of presentation (p=0.04), tumor size (p=0.002), Knosp grading (p=0.001) and cavernous sinus invasion (p<0.001). Among pathological parameters, SSTR2 (n=39,p=0.47), SSTR5 (n=29,p=0.55) and Ki67 (n=46, p=0.23) were not significantly associated with remission, but CAM 5.2 (p=0.07) showed a trend towards significance. Sparsely granular tumours (overall 17.1%) were more likely to be SSTR2 positive (p=0.03) but there was no significant difference in CAM 5.2 positivity as compared to densely granular tumours (p=0.07). On univariate regression analysis, cavernous sinus invasion on MRI (OR 0.04), radiological remission at 3 months (OR 15.7) and low GH nadir on OGTT (OR 0.93) were significant, while on multivariate regression, only cavernous sinus invasion (OR 0.12, 95% CI 0.01-1.32,p=0.08) showed a trend towards significance for remission.

Conclusion: Cavernous sinus invasion predicts remission in acromegaly following TSS. None of the histopathological markers (SSTR2, SSTR5, CAM 5.2) had any impact on outcome. Larger studies are needed to delineate novel markers for outcome prediction in acromegaly.

The authors have no relevant relationships to disclose.

P27

Glucose Intolerance is Driven by Blunted Acute Insulin Response and Not by Decreased Insulin Sensitivity in Patients with Active Acromegaly

Dan Alexandru Niculescu[1,2], Laura Georgiana Zaifu[1], Andreea Kremer[3], Andra Caragheorgheopol[3], Mariana Sava[4], Carmen Iordachescu[4], Roxana Dusceac[2], Iulia Florentina Burcea[1,2], Catalina Poiana[1,2]

[1]Department of Endocrinology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; [2]Department of Pituitary and Neuroendocrine Disorders, C. I. Parhon National Institute of Endocrinology, Bucharest, Romania; [3]Research Laboratory, C. I. Parhon National Institute of Endocrinology, Bucharest, Romania; [4]Biochemistry Department, C. I. Parhon National Institute of Endocrinology, Bucharest, Romania

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Aim: Decreased basal insulin sensitivity (IS) has been repeatedly demonstrated in active acromegaly. However, stimulated insulin secretion has been much less investigated. We aimed to assess stimulated IS and secretion using an intravenous glucose tolerance test (IVGTT) in active acromegaly and healthy controls.

Methods: A 180 min IVGTT was performed in 24 acromegalic patients (13 normal glucose tolerance (NGT), 6 impaired glucose tolerance (IGT) and 5 diabetes mellitus (DM)) and 4 healthy controls. IS was calculated using the slope of the glucose elimination curve and the area under the insulin curve between 0 and 75 min. Acute insulin response (AIRg) was calculated as the area under the insulin curve (above baseline) between 0 and 10 min. No patient was using medical treatment for acromegaly or glucose lowering drugs. The study was approved by the Local Ethical Committee.

Results: NGT had significantly higher serum insulin throughout the test while the serum glucose was lower in the first 10 min and higher after 30 min compared to controls. This translated into a significantly lower IS (0.7 [0.52, 1.16] vs. 2.52 [2.1, 4.0] $(L*10^6)$/pmol*min) and higher AIRg (3963 [3079, 4416] vs. 1692 [1266, 2116] (pmol*min)/L). IGT and DM had significantly higher serum glucose throughout the test compared to NGT. Most glucose intolerant patients (5 IGT and 4 DM) had a characteristic insulin curve with a blunted AIRg (1020 [576, 1520] in IGT and 611 [530, 979] in DM patients) but higher levels after 75 min. There were no significant differences in IS between glucose intolerant and tolerant patients.

Conclusion: Acromegaly with NGT demonstrates reduced IS but compensatory increased insulin response. Most glucose intolerant patients show a characteristic blunted AIRg. These data suggest that in active acromegaly glucose intolerance is due to decreased insulin secretion and not to reduced insulin sensitivity.

The authors have no relevant relationships to disclose.

P28

Growth Hormone/Insulin-Like Growth Factors-I Axis in Atherosclerotic Plaque Stability

[1,2]Salvatore Raia; [1,2]Sabrina Chiloiro; [3]Linda Tartaglione; [4]Federico Biscetti; [1]Antonella Giampietro; [5]Angela Barini; [2]Flavia Angelini; [6]Vincenzo Arena; [2]Laura De Marinis; [1,2]Alfredo Pontecorvi; [4]Andrea Flex; [1,2]Antonio Bianchi

[1]Pituitary Unit, Department of Internal Medicine, Endocrinology and Metabolism, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy; [2]Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy; [3]Unit of Diabetes Care, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [4]Cardiovascular Internal Medicine, Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS; [5]Institute of Biochemistry and Clinical Biochemistry, Department of Laboratory Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [6]Area of Pathology, Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Istituto di Anatomia Patologica, Universita Cattolica Del Sacro Cuore, Rome, Italy

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Background and purpose: cerebrovascular diseases are a major cause of death and several studies found that unstable carotid plaques increased the risk of ischemic stroke. An important role in plaque physiopathology seems to be played by Growth Hormone/Insulin-like Growth Factors-I axis (GH/IGF-I), that acts as anti-oxidant, anti-apoptotic and anti-inflammatory factor. No data are available on this field. Thus, the present study evaluated whether serum GH/IGF-I axis components are associated with internal carotid artery stenosis, defined as high-grade (>70%) carotid stenosis (ICAS), and carotid plaque stability.

Methods: the study included 74 patients with ICAS (mean age 71.9 ± 5,4 years) who underwent a carotid endarterectomy, recruited among subjects consecutively admitted to the Department of Vascular Surgery at the A. Gemelli University Hospital of Rome. We analyzed serum IGF-I, GHBP, IGFBP3. The GHR genotype (fl/fl, fl/d3, or d3/d3) was determined from peripheral blood. Carotid plaques were classified as stable (SP) or unstable (USP) according to the American Heart Association (AHA) criteria

Results: Patients with SP were significantly more frequent in d3/d3-GHR group than other 2 groups (85.7% vs both 62.5% and 52.4% respectively for fl/d3-GHR and fl/fl-GHR carriers, $p<0.05$). Finally, patients were assigned to four groups: patients with USP fl/fl-GHR isoform carriers (Group 1); patients with USP d3-GHR carriers (Group 2); patients with SP fl/fl-GHR isoform carriers (Group 3); patients with SP d3-GHR carriers (Group 4). We found that GHBP and IGF-I plasma levels were significantly higher in Group 4 than Group 1; IGF-I levels were significantly higher also in Group 4 than Group 2.

Conclusions: patients with USP, unlike patients with SP, present a significantly adverse GH/IGF-I components profile according to the GHR genotype.

Only further experimental and clinical prospective studies in larger population will clarify the intriguing role of GH/IGF-I in atherosclerotic plaque.

The authors have no relevant relationships to disclose.

P29

Hyperintensive and Isointensive Tumors are Larger but Less Biochemically Active than Hypointensive- Signal Intensity Ratio in T2 MRI Sequences as Quantitative Approach to Adenoma Intensity Assessment in Patients with Acromegaly

Magdalena Godlewska[1], Anna Grochowska[2], Anna Bogusławska[1], Alicja Hubalewska-Dydejczyk[1], Aleksandra Gilis-Januszewska[1]

Department of Endocrinology, Jagiellonian University Medical College in Cracow, Poland; [2]Department of Radiology, Jagiellonian University Medical College in Cracow, Poland

Introduction: Using adenoma's intensity in T2-weighted pituitary MRI is recommended in everyday management of acromegaly. However, its assessment remains undefined.

Aim: To investigate quantitative and qualitative measurement of somatotroph adenoma's T2-weighted intensity and its clinical implications.

Methods: 116 consecutive patients with acromegaly between 2012-2022 were identified. Dominating cystic adenoma's component or lacking T2-MR images were exclusion criteria, 69 were included in the analysis. Intensity was assessed in: solid part of adenoma, temporal grey matter- visually and qualitatively. Signal Intensity Ratio (SIR) was calculated by dividing adenomas by grey matter's intensity. Hypointensive tumors (HYPO) had SIR <0.8, Isointensive (ISO) 0.8-1.2, Hyperintensive (HYPER) >1.2. The groups were compared in terms of clinical, biochemical and radiological parameters. Subsequently, ROC curve was used to establish cutoff for SIR predicting response to somatostatin analogues(SSA).

Results: Methods classified correspondingly in 74%. HYPER had female predominance (84.6%), not observed in other groups. IGF-1/ULN, GH at baseline and nadir in OGTT didn't differ between groups. Median ratio of GH and tumor volume (ug/l*cm3) was higher for the HYPO than for ISO and HYPER (11.66 vs. 3.7 and 5.56, p=0.048). Median TV (cm3) was higher in HYPER and ISO than in HYPO (2.21 and 1.83 vs. 0.74, p=0.0057). Biochemical control was observed I 10% of HYPER, 29% of ISO and 46% of HYPO (p=0.17). The groups didn't differ in terms of histopathological parameters. ROC curve established the SIR cut-off at 0,738- higher intensity could predict poor response to SSA in 90.91% of cases.

Conclusions: Qualitative and quantitative correspond in 74% of cases. HYPER and ISO are larger but less biochemically active than HYPO. SIR of 0,738 or higher could predict treatment response in majority of cases. Further studies can help create precise, reliable intensity-based prediction marker.

The authors have no relevant relationships to disclose.

P30

Real-world Burden of Medically-treated Acromegaly Patients: The MACRO Registry Experience

Wenyu Huang[1], Murray B. Gordon[2], Kevin Choong Ji Yuen[3], Sara E. Lubitz[4], Roberto Salvatori[5], Maria Fleseriu[6], Adriana Gabriela Ioachimescu[7], Elena A. Christofides[8], Eliza Brevoort Geer[9], Jill Sisco[10], Nienke R. Biermasz[11], Susan D. Mathias[12], Jason A. Crompton[13], Mark E. Molitch[14]

Northwestern University, Chicago, IL, USA[1], Allegheny General Hospital, Pittsburgh, PA, USA[2], Barrow Neurological Institute, Phoenix, AZ, USA[3], Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ[4], Johns Hopkins University School of Medicine, Baltimore, MD, USA[5], Oregon Health & Science University, Portland, OR, USA[6], Medical College of Wisconsin, Hartland, WI, USA[7], Endocrinology Associates, Inc., Columbus, OH, USA[8], Memorial Sloan Kettering, New York, NY, USA[9], Acromegaly Community, Grove, OK, USA[10], Division of Endocrinology, Leiden University Medical Center, Leiden, Netherlands[11], Health Outcomes Solutions, Winter Park, FL, USA[12], Amryt, Boston, MA, USA[13], Northwestern University Feinberg School of Medicine, Chicago, IL, USA[14]

BACKGROUND: The Management of Acromegaly (MACRO) registry is a prospective, observational cohort study of patients with active acromegaly on/eligible for medical therapy with paired data from their treating physicians. The purpose of this analysis is to describe demographics, disease-related information and treatment history of a US-based population.

METHODS: Patients and physicians completed questionnaires at baseline and every 3 months (up to 3 years) regarding demographic, disease activity, treatment information, ratings of symptom and biochemical control, and patient-reported outcomes (PROs) (AcroQOL, Acro-TSQ, and WPAI). Descriptive and kappa (to evaluate concordance between patient and HCP ratings) statistics were calculated.

RESULTS: Data from 199 patients were available (54% female; mean age = 53; mean time since diagnosis = 10 years, 86% post-surgical). Baseline symptoms included joint pain (58%), fatigue (54%), memory problems (43%), sleep apnea (42%), headaches (29%), and sweating (23%). Physicians rated 111/148 (75%) patients on monotherapy, 25/35 (71%) on combination, and 8/16 (50%) on no medical therapy as biochemically well-controlled. Mean (± SD) baseline IGF-I values of physician-rated biochemically well-controlled and partially/not controlled patients were 0.7 (±0.2) x ULN and 1.3 (±0.5) x ULN, respectively.

107/147 (73%) patients with baseline IGF-I ≤ 1 x ULN reported well-controlled symptoms at baseline. Well-controlled symptoms as reported by patients were associated with significantly higher (better) AcroQOL scores across all scales and 5 of 6 Acro-TSQ domains ($p < 0.001$ except injection site interference) and less impairment on 3 of 4 WPAI scales ($p < 0.001$ except absenteeism). Within individual patients, concordance between patient and physician rating of symptom control was low (kappa = 0.231; $p<0.001$).

CONCLUSIONS: Symptom control is an unmet need in acromegaly patients and does not necessarily correlate with biochemical control. Greater consideration should be given to improving symptoms given their significant impact on quality of life, productivity, and activity impairment.

JC receives salary from Amryt; EG receives clinical trial research support from Ionis and Chiasma/Amryt and consulting fees from Chiasma/Amryt; MG receives research support from Amryt and Crinetics and research support and consulting fees from Recordati and NovoNordisk; KY receives consulting fees from NovoNordisk, Ipsen, Amryt, Crinetics, Recordati and Xeris and honoraria from Recordati; MM receives consulting fees from Amryt, Takeda, Sention and Janssen; EC receives consulting fees from Amryt; MF research grants to institution from Amryt, Crinetics and Ionis and consulting fees from Amryt, Camurus, Debiopharm, Ipsen, Recordati and Pfizer; WH receives honoraria and consulting fees from Amryt; RS receives consulting fees from NovoNordisk, Camurus, Recordati and Ipsen; SM receives salary from Health Outcomes Solutions, which received funding from Amryt; AI receives consulting fees from Amryt, Recordati and Camurus; the other authors have no relevant relationships to disclose.

P31

Real-world Use of Oral Octreotide from the Management of Acromegaly (MACRO) Registry

Kevin Choong Ji Yuen[1], Wenyu Huang[2], Murray B. Gordon[3], Maria Fleseriu[4], Eliza Brevoort Geer[5], Takako Araki[6], Artak Labadzhyan[7], Pamela U. Freda[8], Adriana Gabriela Ioachimescu[9], Elena A. Christofides[10], Jill Sisco[11], Nienke R. Biermasz[12], Susan D. Mathias[13], Jason A. Crompton[14], Mark E. Molitch[15]

Barrow Neurological Institute, Phoenix, AZ, USA[1], Northwestern University, Chicago, IL, USA[2], Allegheny General Hospital, Pittsburgh, PA, USA[3], Oregon Health & Science University, Portland, OR, USA[4], Memorial Sloan Kettering, New York, NY, USA[5], University of Minnesota, Minneapolis, MN, USA[6], Cedars-Sinai Medical Center, Los Angeles, CA, USA[7], Columbia College of Physicians & Surgeons, New York, NY, USA[8], Medical College of Wisconsin, Hartland, WI, USA[9], Endocrinology Associates, Inc., Columbus, OH, USA[10], Acromegaly Community, Grove, OK, USA[11], Division of Endocrinology, Leiden University Medical Center, Leiden, Netherlands[12], Health Outcomes Solutions, Winter Park, FL, USA[13], Amryt, Boston, MA, USA[14], Northwestern University Feinberg School of Medicine, Chicago, IL, USA[15]

BACKGROUND: MACRO is a non-interventional, prospective, disease-based cohort registry that collects data on patients with active acromegaly. We report data of real-world experience with oral octreotide capsules (OOC) using paired data from acromegaly patients and their physicians.

METHODS: Patients and physicians completed questionnaires at enrollment and every 3 months (up to 3 years) regarding demographic, disease activity, treatment information, ratings of symptom and biochemical control, and patient-reported outcomes. Descriptive statistics were analyzed.

RESULTS: Out of 215 patients, 31 (14%) were receiving OOC at baseline (28 monotherapy; 3 combination w/pegvisomant) and 26 (12%) initiated post-baseline [21 as monotherapy; 5 combination (2 cabergoline; 1 pegvisomant; 1 pegvisomant/cabergoline; 1 bromocriptine)]. Reasons for initiation of OOC included patient preference (10/25, 40%) and lack of symptom (10/25, 40%) or biochemical control (7/25, 28%). In newly-initiated patients, 5/25 (20%) started OOC at > 40mg/day.

Mean (±SD) time on OOC was 12.5±0.8 months. Last recorded daily dose for patients remaining on OOC monotherapy was 20mg (n=1, 2%), 40mg (n= 20, 45%), 60mg (n=10, 23%), and 80mg (n=12, 27%) or unknown (n=1, 2%). In patients with available IGF-I levels at last follow-up, 84% (36/43) overall and 100% of those remaining on OOC monotherapy were ≤ 1x ULN (mean±SD = 0.9±0.5 for overall group). Of 57 patients receiving OOC at any time, 17 (30%) discontinued therapy [7 (12%), 2 (4%), and 6 (11%) for lack of biochemical control, symptom control or adverse events, respectively]. In OOC monotherapy patients who discontinued for biochemical or symptom control, 4/6 (67%) were receiving < 80mg/day.

CONCLUSIONS: Most patients were receiving OOC as monotherapy at 40mg/day while maintaining or achieving biochemical control. Discontinuation reasons were consistent with clinical trial experience. However, in most patients discontinuing OOC due to inadequate biochemical or symptom control, dose titration to 80mg/day was not completed, suggesting a potential educational need.

JC receives salary from Amryt; EG receives consulting fees from Chiasma/Amryt and clinical trial research support from Ionis and Chiasma/Amryt; MG receives research support from Amryt and Crinetics and research support and consulting fees from Recordati and NovoNordisk; KY receives consulting fees from NovoNordisk, kIpsen, Amryt, Crinetics, Recordati and Xeris and honoraria from Recordati; MM receives consulting fees from Amryt, Takeda, Sention and Janssen; EC receives consulting fees from Amryt; MF receives consulting fees from Amryt, Camurus, Debiopharm, Ipsen, Recordati and Pfizer and research grant to institution from Amryt, Crinetics and Ionis; WH receives consulting and speaker fees from Amryt; SM receives salary from Health Outcomes Solutions, which received funding from Amryt; AI receives consulting fees from Amryt, Recordati and Camurus; the other authors have no relevant relationships to disclose.

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

MISCELLANEOUS

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[18F]FET PET-MRI; A Novel and Accurate Technique for Detection of Small Functional Pituitary Adenomas

Ilanah J. Pruis[1], Frederik A. Verburg[1], Rutger K. Balvers[2], Anita A. Harteveld[1], Richard. A. Feelders[3] , Meike W. Vernooij[1,4], Marion Smits[1,5], Sophie E.M. Veldhuijzen van Zanten[1*], Sebastian J.C.M.M. Neggers[3*]

[1]Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, The Netherlands; [2]Department of Neurosurgery, Erasmus MC, Rotterdam, The Netherlands; [3] Department of Medicine, Section of Endocrinology, Erasmus MC, Rotterdam, The Netherlands; [4]Department of Epidemiology, Erasmus MC, The Netherlands; [5]Medical Delta, Delft, The Netherlands

Background: Small functional pituitary adenomas can cause severely disabling symptoms and early death. The golden standard diagnostic approach includes laboratory tests, MR-imaging +/- inferior petrosal sinus sampling (IPSS). In up to 40% of patients however, the source of excess hormone production remains unidentified or uncertain. This excludes them from surgical and gamma-/cyberknife therapy and adversely affects overall cure rates for patients presenting with Cushing's disease (CD) or acromegaly.

Purpose: To assess the diagnostic yield and accuracy of [18F]FET PET-MRI for detection of small functional pituitary adenoma.

Materials and Methods: In this retrospective study, patients with CD or acromegaly and a suspected primary/recurrent small functional pituitary adenoma, but prior negative/unclear MRI, who underwent [18F]FET PET-MRI between February 1, 2021 and December 1, 2022, were included. Hybrid PET-MRI and MRI-only were evaluated by experienced (nuclear) (neuro-)radiologists and compared with results from previously-obtained MRI, preceding IPSS, post-operative pathology (when performed) and clinical/biochemical follow-up as reference. Diagnostic performance was assessed by calculating sensitivity and positive predictive values (PPV).

Results: Twenty-two CD (79%) and six acromegaly (21%) patients, 68% female, mean age 50±15 years (range: 24–71), were scanned. All CD patients showed focal [18F]FET uptake on PET. The location/lateralization indicated by IPSS corresponded with PET-MRI in only 7/17 (41%). In 11/14 patients who underwent surgery, a pituitary adenoma was confirmed by pathology (n=11) and/or biochemical remission (n=11) rendering a sensitivity of 100% and estimated PPV between 79–100%. Four acromegaly patients (67%) had a positive [18F]FET PET and 1/1 patient showed biochemical remission after surgery.

Conclusion: [18F]FET PET-MRI shows a high diagnostic yield and accuracy for localizing small functional pituitary adenoma, exceeding results of MRI-only +/- IPSS. This multimodal imaging technique provides a welcome improvement for diagnosis clinical outcome of patients and resulting in a high short-term remission rate of 79% in CD patients.

SJCMMN has no relevant relationships to disclose.

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An International, Simulated-use Study Assessing Nurses' Preferences Between Two Lanreotide Syringes (Somatuline Autogel vs Pharmathen) for the Treatment of Acromegaly and/or Neuroendocrine Tumours (NETs): PRESTO 3

D Ferone,[1,2] W Martin,[3] J Williams,[4] A Houchard,[5] C Pommie,[5] A Ribeiro-Oliveira Jr,[6] A B Grossman,[7,8]

[1]IRCCS Ospedale Policlinico San Martino, Genova, Italy; [2]Department of Internal Medicine and Medical Specialties, University of Genova, Genova, Italy; [3]Kings College Hospital Foundation Trust, London, UK; [4]Oregon Health and Science University Pituitary Center, Portland, OR, USA; [5]Ipsen, Boulogne-Billancourt, Paris, France; [6]Ipsen, Cambridge, MA, USA; [7]Green Templeton College, University of Oxford, Oxford, UK; [8]Neuroendocrine Tumour Unit, ENETS Centre of Excellence, Royal Free Hospital, London, UK

Introduction/Background: Somatostatin analogues (SSAs) represent the mainstay of treatments for patients with acromegaly and NETs. Confidence in and ease of use of syringes used to administer SSAs is important for decision-making in long-term therapy.

Aims: PRESTO 3 compared nurses' preference for the Somatuline Autogel syringe versus the Pharmathen syringe after injection-pad testing. We report preferences for 11 attributes.

Methods: This simulated-use study included oncology/endocrinology nurses (planned sample size 92) with ≥1 year experience in managing acromegaly and/or NETs. Nurses tested both syringes twice in a randomised order, before completing an electronic preference survey. The primary objective was to assess overall preference (%, 95% confidence interval [CI]) for the Somatuline Autogel syringe versus the Pharmathen syringe, tested using a one-sample exact binomial test. Secondary objectives included rating performance (scored from 1 [not at all] to 5 [very much]; Wilcoxon 2-sided signed-rank test) and ranking importance of syringe attributes.

Results: Ninety-four nurses were enrolled: mean age, 41.0 (SD, 11.5) years; 72.3% in Europe, 27.7% in the USA. The proportion of nurses stating a preference ('strong' or 'slight') for the Somatuline Autogel syringe [86.2% (95% CI 77.5%–92.4%)] was statistically significantly higher than 50% ($p<0.0001$). The syringe attributes considered most important were "Easy to use from preparation to injection" (30.9%) and "Comfortable to handle during use from preparation to injection" (20.2%). The attribute most commonly rated as least important was "Fast administration from preparation to injection" (26.6%). Performance rating was statistically significantly higher with Somatuline Autogel than the Pharmathen syringe for 10/11 attributes ($p<0.05$).
Conclusions: Nurses strongly preferred the user experience of the Somatuline Autogel syringe over the Pharmathen syringe. "Ease of use" and "comfortable to handle" were considered the most important syringe attributes, and performance rating was significantly higher with Somatuline Autogel than the Pharmathen syringe for all but one attribute.

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FDG-PET Does Not Help Distinguish Benign from Malignant Pituitary Lesions

Alexandra J. White[1], Joshua L. Golubovsky[2], Roger Murayi[1], Erion Junior de Andrade[1,3], Peter Ahorukomeye[4], Diana C. Lopez[1], Christopher J. Karakasis[5], Varun R. Kshettry[1,3], Pablo F. Recinos[1,3]

[1]Department of Neurosurgery, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA; [2]Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA, USA; [3]Section of Skull Base Surgery, Rose Ella Burkhardt Brain Tumor & Neuro-Oncology Center, Cleveland Clinic Foundation, Cleveland, OH, USA; [4]Case Western Reserve University School of Medicine, Cleveland, OH, USA; [5]Imaging Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

Introduction: When a new pituitary lesion is discovered on imaging in a patient with cancer, differentiating between a pituitary adenoma and a metastasis poses a significant diagnostic challenge. Likewise, a pituitary lesion with indeterminate features on MRI may prompt a PET scan for further characterization.

Objective: We aimed to investigate if maximum standardized uptake value (SUVmax) on PET scans was helpful in differentiating between pituitary adenomas and metastases.

Methods: The electronic medical records of patients with pituitary lesions who underwent FDG-PET scans and were seen at our institution from 1995 to 2022 were reviewed. Clinical history, imaging features, and management details were collected.

Results: Forty-four patients met inclusion criteria. Five (11%) had metastases as identified by imaging characteristics alone (e.g., thickened pituitary infundibulum, rapid size increase, rapidly progressive osseous destruction), 28 (64%) had pituitary adenomas based on imaging characteristics alone, one (2%) had Langerhans cell histiocytosis based on pituitary imaging and biopsy of a femoral lesion, two had hypophysitis based on imaging, and one (2%) had an arachnoid cyst. The SUVmax values of the metastatic lesions were 5.1, 8.7, 21.9, 11.5, and 20 (mean 13.4). SUVmax values in pituitary adenomas were similar (mean 15.1) ($p = 0.65$). The lesion due to Langerhans cell histiocytosis had an SUVmax of 4.1. The lesion due to an arachnoid cyst had an SUVmax of 3.08. The lesions due to hypophysitis had SUVmax values of 3.2 and 9.3.

Conclusion: Maximum SUV was not a reliable metric for differentiating between malignant and benign pituitary lesions in our series. While PET scans can identify pituitary lesions, they were not helpful in differentiating their etiology. Clinicians should take this into account in their workup of newly diagnosed pituitary lesions.

The authors have no relevant relationships to disclose.

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Hypopituitarism in Transfusion-Dependent Beta Thalassemia and its Association with Pituitary Siderosis

Pinaki Dutta[1], Liza Das[1,2], Alka Khadwal[3], Chirag Kamal Ahuja[4], Pankaj Malhotra[3], Paramjeet Singh[4], Sanjay Kumar Bhadada[1]

Departments of [1]Endocrinology, [2]Telemedicine, [3]Hemato-oncology & Medical-Oncology, [4]Radiodiagnosis, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Introduction: Thalassemia-related hypopituitarism is an infrequently recognised entity, despite beta thalassemia (β-TM) being the most commonly inherited hemoglobinopathy. We aimed to assess the burden of pituitary insufficiency in a cohort of transfusion-dependent ƙ-TM patients.

Patients and Methods: Patients with β-TM (n=48) were recruited in the study. Hypothalamo-pituitary-adrenal, thyroid, gonadal axes, and lactotroph function were evaluated. Hormone levels, including serum cortisol, ACTH, DHEAS, T3, T4, TSH, prolactin, IGF-1, LH, FSH, testosterone, and estradiol were estimated in a fasting sample (0800-0900h) under appropriate cold-chain conditions by electro-chemiluminescence assay (ECLIA, COBAS 8000, Roche Diagnostics, Germany) just before blood transfusion. MRI was performed to assess the presence and severity of organ-specific siderosis (cardiac, hepatic, pituitary) using T2 weighted and unenhanced coronal and axial HASTE followed by GRE sequences.

Results: The mean age of the cohort was 26.7 ± 6.6 years, and the mean age at initiation of blood transfusion was 4 (3-7) months. All patients were transfusion-dependent, with a mean annual requirement of 20 ± 9 units blood. Hypothalamo-pituitary insufficiency was prevalent in 95.7%, with multiple pituitary axes deficiency (≥3) in 23.4%. Secondary hypogonadism and low IGF-1 were the most frequent (60.4% each), followed by hypothyroidism (41.7%) and hypocortisolism (39.5%). Ongoing chelation therapy was either in the form of deferasirox (61.5%) or deferiprone (38.5%). Hepatic siderosis was more common than cardiac siderosis (76.6% vs 38.3%). MRI sella revealed greater prevalence of pituitary T2 hypointensity (67.7%) than loss of volume (36.3%). Calvarial thickening was frequent (84.8%). There was no association between the prevalence of hypopituitarism and pituitary iron deposition (p=0.91) or reduced pituitary volume (p=0.68).

Conclusion: Hypopituitarism is highly prevalent in transfusion-dependent thalassemia, with multiple hormone deficiencies affecting nearly every fourth patient. Pituitary T2 hypointensity is more common and likely predates loss of pituitary volume, despite no association between either parameter and hypopituitarism.

The authors have no relevant relationships to disclose.

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Patient and Caregiver Perspectives of Fluid Discharge Protocols Following Pituitary Surgery

Julia Chang[1], Alexis Amano[2], Cati Brown Johnson[2], Olivia Chu[3], Victoria Gates-Bazarbay[3], Erin Wipff[3], Samantha MR Kling[2], Juan Carlos Fernandez-Miranda[4], Stacie Vilendrer[2]

Division of Endocrinology, Gerontology, and Metabolism, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA[1]; Division of Primary Care and Population Health, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA[2]; Neuroscience Health Center, Stanford Health Care, Palo Alto, CA, USA[3]; Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA, USA[4]

Objective: Short-term post-operative fluid restriction after transsphenoidal surgery (TSS) for pituitary tumors may effectively prevent delayed hyponatremia, the most common cause of readmission. However, implementation of individualized fluid restriction interventions after discharge is often complex and poses challenges for provider and patient. The purpose of this study was to understand the factors necessary for successful implementation of fluid restriction and discharge care protocols following TSS.

Methods: Semi-structured interviews with fifteen patients and four caregivers on fluid discharge protocols were conducted following TSS. Patients and caregivers who had surgery before and after the implementation of updated discharge protocols were interviewed. Data were analyzed inductively using a procedure informed by rapid and thematic analysis.

Results: Most patients and caregivers perceived fluid restriction protocols as acceptable and feasible when required. Facilitators to the protocols included clear communication about the purpose of and strategies for fluid restriction, access to the care team, and involvement of patients' caregivers in care discussions. Barriers included patient confusion about differences in the care plan between teams, physical discomfort of fluid restriction, increased burden of tracking fluids during recovery, and lack of clarity surrounding desmopressin prescriptions.

Conclusion: Outpatient fluid restriction protocols are a feasible intervention following pituitary surgery but requires frequent patient communication and education. This evaluation highlights the importance of patient engagement and feedback to effectively develop and implement complex clinical interventions.

The authors have no relevant relationships to disclose.

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Pituitary Adenomas in the Elderly: A Report of Two Cases

Lees F.[1], Risso M.[1], Lima, R.[2], Garagorry, F.[3], Ricagni L.[4], Piñeyro M.[1]

[1]Clinica de Endocrinologia y Metabolismo, Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay; [2]Neurocirugía, Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay; [3]Anatomía Patológica, Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay; [4]Cátedra de Oncología Radioterápica,Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

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Introduction: The reported prevalence of pituitary adenomas in the elderly (≥65 years) is about 10%-20%, but may be currently underestimated. We present two clinical cases of pituitary adenomas in the elderly.

Case 1: A 67-year-old male, a pituitary adenoma was found on CT scan due to head trauma. He presented with a history of visual field defects of several months and gait unsteadiness. He did not have any symptoms or signs of pituitary hormone dysfunction. Pituitary MRI reported a 58 mm x 37 mm x 36 mm sellar mass, with suprasellar extension, with optic chiasmal compression. Pituitary hormone evaluation was normal. Transsphenoidal surgery was performed and a non-functioning pituitary adenoma (NFPA) was diagnosed by immunohistochemistry.

Case 2: An 81-year-old female presented with a history of one month of functional decline. A pituitary incidentaloma was found on head CT scan. Pituitary MRI showed a 30 mm x 23 mm x 34 mm sellar mass with bilateral cavernous sinus invasion. Hyperprolactinemia due to stalk effect was found (diluted prolactin of 120 ng/mL) and secondary hypothyroidism. A presumptive diagnosis of NFPA was made. Due to high perioperative risk no surgery was performed.

Discussion: The prevalence of pituitary adenomas in the elderly is rising due to longer life expectancy and better health care, as well as the increase in incidental imaging findings. A higher prevalence of non-functioning pituitary adenomas in this age group has been reported. Most common symptoms of presentation are visual field defects, headaches and hypopituitarism. Optimal management should take into account clinical presentation, tumor size and patient clinical status and co-morbidities.

Conclusions: Pituitary adenomas in the elderly can represent a diagnostic and therapeutic challenge. Further studies on the natural history and behavior of pituitary adenomas in the elderly are warranted to optimize treatment and quality of life.

The authors have no relevant relationships to disclose.

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RAPID, a Multicenter United States Pituitary Surgery Research Consortium, Surpasses 2000 Enrolled Patients and Identifies Surgery Quality Improvement Opportunities

Michael Karsy[1], Andrew S. Little[2], James Evans[3], Won Kim[4], Donato Pacione[5], Albert Kim[6], Paul Gardner[7], Benjamin Hendricks[2], Christina Sarris[2], Ildiko Torok[2], Trevor Low[2], Tomiko Crocker[2], Benita Valappil[7], Mridu Kanga[6], Hussein Abdallah[7], Sarah Collopy[3], Douglas Hardesty[8], Vera Vigo[9], William Delery[4], Kevin Yuen[2], Carolina Benjamin[10], Varun Kshettry[11], Michael Chicoine[6]

Drexel University, Philadelphia, PA, USA[1], Barrow Neurological Institute, Phoenix, AZ, USA[2], Jefferson University, Philadelphia, PA, USA[3], University of California, Los Angeles, Los Angeles, CA, USA[4], New York University, New York, NY, US [5], Washington University, St Louis, MO, USA[6], University of Pittsburgh Medical Center, Pittsburgh, PA, USA[7], The Ohio State University, Columbus, OH, USA[8], Stanford University, Palo Alto, CA, USA[9], University of Miami, Miami, FL, USA[10], Cleveland Clinic Foundation, Cleveland, OH, USA[11]

Introduction: Establishing a national pituitary surgical research consortium is essential to improving patient care by evaluating patient outcomes, developing benchmarks, and disseminating best practices. Furthermore, such collaboration facilitates multicenter surgery research at scale for these uncommon diseases. We describe the first United States pituitary surgery research platform, Registry of Adenomas of the Pituitary and related Disorders (RAPID), report patient outcomes to date, and explore quality improvement opportunities to share with the community.

Methods: RAPID was founded in 2021 and has grown to include 11 United States academic pituitary centers. Organizational bylaws and data sharing agreements were executed between sites, and a data coordinating center was established. Ethics approval was obtained at participating sites. Nonfunctioning adenoma, prolactinoma, acromegaly, Cushing's disease, and Rathke's cleft cyst clinical modules were created. Surgical data were aggregated using a HIPAA compliant cloud-based platform. Patients treated prior to creation of RAPID were enrolled in the retrospective cohort, and subsequent patients were enrolled in the prospective cohort. A steering committee coordinated group activities.

Results: 2232 surgical patients have been enrolled to date. The cohort contains 1292 patients with nonfunctioning pituitary neuroendocrine tumors, 517 with Cushing's disease, and 219 with acromegaly from 24 neurosurgeons and 21 otolaryngologists. The average length of stay after transsphenoidal surgery was 2.8±3.4 days. 90-day unplanned readmission rate was 8.7% (67/766). 97.9% (1079/1102) patients were discharged home. There was one (1/1038, 0.1%) perioperative death from respiratory failure in a morbidly obese patient with Cushing's disease. The average length of follow-up was 3.6±3.8 years.

Conclusions: This large study from a U.S. research consortium demonstrates opportunities to improve length of stay, unplanned readmission rates, and reduce outcomes variability following pituitary surgery. Future initiatives include growing prospective patient enrolment and developing surgical quality outcomes milestones for pituitary centers to use as a guide for quality improvement.

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The Incidence and Tumor Features of Plurihormonal Pituitary Adenomas

Michelle D. Lundholm, Divya Yogi-Morren

Cleveland Clinic Endocrinology & Metabolism Institute, Cleveland, OH, USA

INTRODUCTION: Plurihormonal pituitary adenomas (PPAs) co-stain for more than one pituitary cell line and are capable of secreting two or more pituitary hormones. Given a paucity of information on PPAs, we report the incidence and tumor features associated with PPAs at a large tertiary referral center.

METHODS: A single-center retrospective chart review was conducted on consecutive patients with pathology-proven pituitary adenomas following resection from 2003-2018 with IRB approval. PPAs were identified by co-staining for two or more cell lines by antibodies to prolactin (PRL), growth hormone (GH), adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), luteinizing hormone (LH), or follicular stimulating hormone (FSH). Descriptive statistics were used.

RESULTS: Of 1,080 surgical pituitary adenoma cases, 5.8% (N=63) PPAs were identified for inclusion. The median patient age was 52yrs (range 18-77yrs), 39.7% (N=25) female, with median tumor size 2cm (range 0.2-7cm in largest dimension). All tumors were benign. The most common patterns of co-staining were GH-TSH in 28.6% (N=18) and GH-PRL in 22.2% (N=14). The majority 66.6% (N=42) of tumors had cell lines originating from the same progenitor cells. Only 7.9% (N=5) of PPA cases had co-secretion of hormones (GH-PRL in N=3, GH-TSH in N=1, and ACTH-PRL in N=1), and 40.0% (N=25) were non-functional. The most commonly secreted pituitary hormone was GH associated with acromegaly in 55.6% (N=35). Other hormones were secreted in <8% of PPA cases.

DISCUSSION/CONCLUSION: Approximately 1 in 20 resected pituitary adenomas was a PPA, and most shared common progenitor cells regulated by the same transcription factors. The most common PPAs contained a combination of somatotropic, lactotropic, or thyrotropic cells regulated by PIT-1. PPAs rarely co-secrete; if anything, most secreted GH. PPA tumors would be missed if immunohistochemical analysis were not performed on all resected pituitary adenomas. Further study is needed to understand the pathogenesis and clinical implications of PPAs.

The authors have no relevant relationships to disclose.

PITUITARY FUNCTION

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A Novel Approach to Hypophysitis: Outcomes Using Non-Steroidal Immunosuppressive Therapy

Ilan Remba-Shapiro[1]; Janaki D. Vakharia[1]; Maged Muhammed[1]; Marcela Marsiglia[2]; Bart Chwalisz[3,4]; Lisa B. Nachtigall[1]

Neuroendocrine Unit, Division of Endocrinology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA[1], Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA[2], Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA[3], Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, USA[4]

Objective: To determine the pituitary function before and after non-steroidal immunosuppressive therapy (NSIT) in subjects with hypophysitis and evaluate their clinical and radiologic outcomes.

Methods: This retrospective, longitudinal study was approved by the Institutional Review Board. We reviewed a large database, selected subjects with hypophysitis treated with NSIT, and collected information on the duration of therapy, clinical, hormonal, and radiologic outcomes. Normally distributed and non-normally distributed data was reported as mean ± standard deviation and median with interquartile ranges, respectively. Paired t-test was used to assess mean pituitary stalk thickness before and after NSIT. A p value <0.05 was considered statistically significant.

Results: Twelve subjects met inclusion criteria. Five subjects had primary hypophysitis (PH), while seven had secondary hypophysitis (SH) due to an underlying systemic inflammatory disease. Mean age ± SD was 48.0±15.7 years and 40.9±13.0 years, for PH and SH respectively. The majority were female (PH 60% and SH 86%). BMI ± SD at presentation was 25.2±2.5 kg/m2 and 26.8±6.7 kg/m2 for PH and SH, respectively. The most common symptom at presentation was fatigue (75%). All PH subjects (100%) and 2 (28.6%) SH subjects had polyuria/polydipsia. There was a significant decrease in mean stalk thickness after NSIT (p=0.0051) (mean duration 16.5±4.8 months). Three subjects had changes in pituitary hormone function during the course of NSIT: one recovered vasopressin, one developed growth hormone deficiency, and another became hyperprolactinemic. Mycophenolate mofetil was the most used NSIT; adverse effects prompted discontinuation in 2/7 patients.

Conclusions: Subjects with hypophysitis receiving non-steroidal immunosuppressive therapy had stable or improved brain/pituitary MRI findings with significant decrease in pituitary stalk thickness. Few had changes in pituitary function during the treatment course, which was generally well tolerated. Our findings suggest that non-steroidal immunosuppressive therapy may be considered as an alternative therapy for patients with hypophysitis who require immunosuppression.

The authors have no relevant relationships to disclose.

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A Successful Long-Time Experience of a Dose-Finding Approach for the Treatment of Central Adrenal Insufficiency (CAI)

Silvia R Correa-Silva; Pedro F Santos-Neto; Bruna M Mascarenhas-Nakano; Julio Abucham

Neuroendocrine Unit, Endocrinology Division, Escola Paulista de Medicina –Unifesp, Sao Paulo, Brazil

Introduction: Hydrocortisone (HC) is considered the preferred treatment for patients with CAI. Doses in the upper part of the previously suggested range have been associated with higher cardiovascular morbimortality and recommended doses have been reduced. In our country, HC has never been available in tablets, whereas prednisone, is available in 5mg and 20mg tablets (lower doses are available elsewhere), is easily found, has a low cost, and doesn't require prescription.

Aim: To analyze our experience with prednisone in patients with CAI using the same dose-finding protocol established four decades ago.

Patients: Data were extracted from electronic files. Seventy-two patients entered the study. Inclusion criteria: >18y, last consultation <2y, stable/same daily doses of prednisone, replacement of thyroid and sex hormone deficits. Exclusion criteria: Cushing´s disease, non-controlled acromegaly, malabsortion, glucocorticoid-requiring diseases, hepatopathy.

Dose-finding protocol: Starting doses of prednisone are 2.5mg or 5.0mg. Thereafter, adjustments are done according to clinical signs/symptoms. A pre-defined minimal dose (2.5mg) is attempted in all patients. Patients requiring >2.5mg are changed to 5.0mg, and then suggested 3.75mg (3/4 of a 5.0mg tablet). If the 3.75mg is insufficient, return to 5.0mg; if unpractical, we suggest alternating (2.5/5.0mg) or 5.0mg doses.

Statistical analysis: Patients were divided in two dose groups. Statistics: Student´s t-test and Fisher´s exact test. $P<0.05$: significant.

Results: Fifty-four patients on 2.5mg (75%) and 18 patients on 5.0mg (25%). None was on GH replacement. The 5mg group tended to be younger (P=0.06).

No significant differences (0.10<P<1.0) were found in: sex, treatment duration, BMI (at diagnosis and last visit), hormone deficiencies, IGF-1 levels, diabetes, dyslipidemia, and hypertension between groups.

Conclusions: Patients with CAI are successfully treated with a low morning dose of prednisone. A dose-finding approach is able to adjust doses close to individual requirements. Intermediate and <2.5mg doses should be tried where low dose tablets are available.

The authors have no relevant relationships to disclose.

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Incidence of Postoperative Hyponatremia After Endoscopic Endonasal Pituitary Transposition for Skull Base Pathologies

Francesca Galbiati[1*], Sharini Venugopal[2*], Hussam Abou-Al-Shaar[3], Georgios A. Zenonos[3], Paul A. Gardner[3], Pouneh K. Fazeli[2], Hussain Mahmud[2]

[1]Department of General Internal Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [2]Neuroendocrinology Unit, Division of Endocrinology and Metabolism, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [3]Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Objective: Pituitary transposition is a novel surgical approach to access the retroinfundibular space and interpeduncular cistern. Few studies have evaluated post-surgical outcomes, including incidence of hyponatremia, following pituitary transposition.

Methods: This is a retrospective study including 72 patients (57% females, age 45.51±17.55 years) who underwent endoscopic endonasal surgery involving pituitary transposition for non-pituitary derived tumors over a decade at the University of Pittsburgh Medical Center. Anterior pituitary deficiencies and replacement therapy, tumor pathology and pre-operative serum sodium (Na) were recorded. Na was assessed at postoperative day 1, 3, 5, 7, and 10. Na nadir in the first 21 days post-operatively was recorded. T-test (normally distributed variables) and Wilcoxon rank-sum test (not-normally distributed) were applied for mean/median comparison.

Results: 55.6% patients developed post-operative hyponatremia. Two patients (5%) developed severe hyponatremia (sodium level <120 mmol/L). 11/72 (15.3%) patients required desmopressin replacement post-operatively, and all patients had transient arginine vasopressin deficiency (AVD, formerly diabetes insipidus). Two (2.8%%) patients were on diuretic therapy prior to surgery and 25 (34%) received postoperative diuretics (acetazolamide, 21 patients and furosemide, 4 patients). No difference in the risk of hyponatremia was noted with diuretic use (p=0.658).

Conclusion: For the first time, this study showed that more than half of patients who had pituitary transposition developed hyponatremia, that was not related to perioperative diuretic use. Post-operative AVD rate was similar to previously reported rates after pituitary surgery. Larger, longitudinal studies are needed to determine risk-stratification factors for post-operative hyponatremia following pituitary transposition.

The authors have no relevant relationships to disclose.

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Intrasellar Arachnoid Diverticula in Patients with Sellar Pathology: Association with Intraoperative Cerebrospinal Fluid Leak in Patients Undergoing Endoscopic Transsphenoidal Surgery

Sauradeep Sarkar, Edward R. Laws, Timothy R. Smith

Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Objective: Intraoperative cerebrospinal fluid (CSF) leakage is a frequently reported morbidity following transsphenoidal resection of sellar-suprasellar pathology. An intrasellar arachnoid diverticulum can often be identified on preoperative imaging in patients undergoing endoscopic transsphenoidal surgery. The objective of this study was to evaluate arachnoid diverticulae as a risk factor for intraoperative CSF leak in a large institutional cohort of patients with pituitary tumors and cysts.

Methods: A retrospective analysis of 619 patients who underwent 638 endoscopic transsphenoidal operations from 2013-2022 was performed. Preoperative T1- and T2-weighted mid-sagittal MRI studies were examined both quantitatively and qualitatively for the presence of an arachnoid diverticulum, which was considered significant if its vertical depth exceeded 50% of the sellar height. These were classified as Type 1 (ventral CSF cleft with no tumor/gland tissue between sellar face and infundibulum) or Type 2 (central CSF cleft with tumor/gland tissue between sellar face and infundibulum).

Results: A significant arachnoid diverticulum was identified in 79 cases (12.4%), and its presence was associated with younger age (p=0.041), higher BMI (p=0.018), prior transsphenoidal surgery (p<0.001) and smaller tumor size (p<0.001). The incidence of intraoperative CSF leak was higher in patients with significant arachnoid diverticulae (55.7% versus 23.4%; p<0.001). There was a higher incidence of intraoperative CSF leak in cases with Type 1 clefts as compared to Type 2 clefts (58.8% versus 36.4%; p=0.201). The overall intraoperative CSF leak rate was 27.4%; and CSF leaks were independently associated with age ≥65 years (p=0.003), cystic pathology (p=0.015) and the presence of a significant arachnoid diverticulum (p<0.001) on logistic regression analysis.

Conclusions: The presence of an intrasellar arachnoid diverticulum should alert the surgeon to an elevated risk of intraoperative CSF leak. A relatively limited exposure tailored to the craniocaudal extent of the sellar pathology should be considered in these patients.

The authors have no relevant relationships to disclose.

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Morphologic Classification of Pituitary Macroadenomas with Suprasellar Extension: Impact on Surgical Outcomes

Sauradeep Sarkar, Edward R. Laws, Timothy R. Smith

Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Objective: To study the association between various morphologic parameters and surgical outcomes in pituitary macroadenomas with suprasellar extension.

Methods: Magnetic resonance imaging (MRI) studies of 160 patients undergoing endoscopic transsphenoidal resection of pituitary macroadenomas with suprasellar extension were reviewed. In the coronal plane, tumors were classified into Type 1 (dome-shaped; no constriction at level of diaphragma sellae) and Type 2 (dumbbell-shaped; with constriction at level of diaphragma sellae. Based on the dome-to-neck (D/N) ratio, Type 2 tumors were further classified as Type 2A (wide-neck; D/N 1-1.3) and Type 2B (narrow-neck; D/N ≥1.3). In the sagittal plane, the ventral (Vsuprasellar) and dorsal (Dsuprasellar) angles subtended by the suprasellar component of the tumor with the tuberculum-dorsum line were also used to separately classify tumors. Surgical outcomes and complications were analyzed using a logistic regression model. Extent of resection (EOR) was assessed in all patients with available postoperative MRI (n=149).

Results: There were 108 Type 1 tumors, and 26 patients each in the Type 2A and 2B sub-groups. Tumor subtype was significantly associated with tumor size (p<0.001), intraoperative CSF leak (p<0.001), extent of resection (p<0.001), postoperative suprasellar residual tumor (p<0.001), and postoperative complications including diabetes insipidus (DI, p=0.005) and visual worsening (p=0.003). On multivariate analysis, after adjusting for confounders, Type 2B tumors were associated with EOR (OR 0.216; 95% CI 0.069-0.676; p=0.008), presence of suprasellar residual tumor (OR 18.081; 95% CI 5.198-62.889; p<0.001), intraoperative CSF leak (OR 5.328; 95% CI 1.894-14.985; p=0.002) and postoperative DI (OR 4.889; 95% CI 1.666-14.348; p<0.001). Acute (<90 degrees) Vsuprasellar and Dsuprasellar angles were also each associated with EOR, intraoperative CSF and visual complications after surgery.

Conclusions: Preoperative tumor classification based on D/N ratio is surgically relevant, and Type 2B macroadenomas are significantly associated with lower rates of GTR and higher complication rates following transsphenoidal resection.

The authors have no relevant relationships to disclose.

PROLACTIN/PROLACTINOMA

P45

A 14-year Review and Assessment of Patients with Prolactinomas, Treated Surgically

Edward Laws, Sherry Iuliano

Department of Neurosurgery, Brigham and Women's Hospital, Boston, MA

Introduction: This study reviews 106 patients with signs and symptoms of Prolactin secreting Pituitary Adenomas, treated surgically at the Brigham and Women's Hospital in Boston, MA. from 2008 through 2022. These 106 patients met our criteria for transsphenoidal endoscopic surgery for resection of Pituitary lesions associated with excessive levels of Prolactin.

Objectives: The goal of this study was to investigate the presentation, clinico-pathologic aspects, and outcomes from this type of treatment for patients with Prolactinomas.

Patients and methods: The patient cohort consisted of 62 women and 44 men, for a total of 106 individuals. The age ranges of our patients were from age 16 to age 68. Comprehensive Endocrine evaluation of all patients was carried out by our colleagues from Endocrinology, and appropriate laboratory tests for Pituitary hormones, and neuroimaging testing by MRI was obtained for all. The possibility of medical therapy was discussed with the patients, and the alternatives of care were described in detail. Among our patients there were 24 who were previously treated with Cabergoline, and who had either intolerance, lack of efficacy, or unpleasant side effects that prompted the consideration of surgical treatment.

Results: The sizes of the lesions included the following: 60 macroadenomas, 42 microadenomas, 3 "giant" adenomas, and 1 case that was a tumor destroyed by apoplexy.

Our Pathologists carefully studied the nature of the tumor tissue removed at surgery. There were 86 tumors staining for Prolactin alone; there were 14 tumors that stained both for Growth Hormone and Prolactin, there were 2 MST tumors and one tumor staining for both TSH and Prolactin. Those patients with GH/PRL or MST tumors often had some persistent acromegaly. There was one "silent" tumor, and there were 2 lesions that consisted of cyst tissue only. Among all the patients, there were 18 cystic tumors, 16 invasive tumors, and 5 that had evidence of prior Pituitary tumor apoplexy. Eight patients had visual loss; when the bulk of the tumor was enough, sometimes along with invasion, to produce visual loss, which was frequently reversed with appropriate resection of the lesions. It should be noted that prior Surgery at other institutions had been given to 12 of our patients.

Conclusions: Regarding complications of surgery in our patients, there were 2 patients who developed epistaxis in the immediate postoperative recovery process, and this was readily corrected by our ENT colleagues. We had 2 cases of transient diabetes insipidus following surgery, effectively treated, and the patients recovered. There were no spinal fluid leaks, and very little in the way of postoperative hypopituitarism requiring additional hormonal therapy. No other surgical morbidity was encountered.

Because many of our patients were from areas not close to Boston, our follow-up evaluation is somewhat limited; 23 patients were lost to our follow-up care. At follow-up, most patients had normal prolactin levels, but at least 35 patients required treatment with Cabergoline to normalize their Prolactin levels and their associated symptoms. This 14-year experience has generally been very satisfactory for the patients, and also for their Endocrinologists, Surgeons and Physicians.

The authors have no relevant relationships to disclose.

P46

Anti-Tumor Effect of Rosiglitazone Via Upregulating 15-PDGH in Prolactin Secreting Adenoma

Chan Woo Kang[1]; Ju Hun Oh[1]; Eun Kyung Wang[1]; Soohyun Lee[1]; Jung Ho Nam[1]; Youngsook Kim[1]; Jae Won Hong[2]; Eun Jig Lee[1]; Cheol Ryong Ku[1]

[1]Endocrinology, Institute of Endocrine Research, College of Medicine, Yonsei University, Seoul, Korea; [2]Department of Internal Medicine, Inje University Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Republic of Korea

Background: Rosiglitazone, a synthetic peroxisome proliferator-activated receptor γ (PPAR γ) ligand, are used to treat type II diabetes. Over the last few years, PPAR γ has received much attention for its ability to exert variable tumors.

Objective: The aim of this study is to investigate the anti-tumor effect of rosiglitazone on prolactin secreting pituitary adenomas and its mechanism.

Materials & Methods: Lactotroph cell line (GH4, MMQ) were treated with Phosphate-buffered saline (PBS) or rosiglitazone. In vitro analysis such as qPCR, immunoblot, prolactin (PRL) ELISA, Cell proliferation assay, and Fluorescence-activating cell sorting (FACS) analysis were performed to examine the effect of rosiglitazone on Lactotroph cell lines.

Result: To investigate the direct effect of rosiglitazone on PRL secretion of the pituitary adenomas, GH4 and MMQ cells were treated with rosiglitazone 1, 5, 10, 50 μM for 72 hr. Both PRL mRNA and secretion levels were significantly decreased by rosiglitazone in a dose-dependent

manner. In previous studies, 15-PDGH has been implicated as a tumor suppressor gene with the property that inhibits the tumor growth. Interestingly, 5 μM rosiglitazone upregulated the mRNA and protein levels of 15-PDGH in both GH4 (4.73-fold) and MMQ (4.04-fold) cells. Next, we investigated whether rosiglitazone had any effects on the proliferation of prolactinoma cells. Proliferation of the GH4 and MMQ cells were significantly decreased by rosiglitazone in a dose-dependent manner after treatment. Rosiglitazone potently induced cell cycle arrest in sub-G1inGH4 and MMQ cells. Furthermore, rosiglitazone treatment significantly increased both early (2.31-fold) and late apoptosis (1.9-fold) of GH4 and MMQ cells.

Conclusion: These results collectively position 15-PDGH as a potential new therapeutic target for prolactinomas and implicate rosiglitazone as a possible alternative pharmacological approach for prolactinomas.

The authors have no relevant relationships to disclose.

P47

Genomic Analysis of Prolactinomas Identified Genetic Drivers and Recurrent Copy Number Variation

Ticiana Paes[1]; Dipika R Mohan[2]; Jocobo Buelvas Mebarak[1]; Wenya Linda Bi[3]; Rona S. Carroll[1]; Ursula B. Kaiser[1]; Antonio Marcondes Lerario[3]; Ana Paula Abreu[1]

[1]Department of Medicine, Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [2]Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA; [3]Center for Skull Base and Pituitary Surgery, Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [4]Department of Internal Medicine, Division of Metabolism, Endocrinology, and Diabetes, University of Michigan, Ann Arbor, MI, USA

Introduction: Prolactin-secreting adenomas (prolactinomas) are the most common type of pituitary adenomas. Although the SF3B1 p.R625H mutation has been associated with prolactinomas, their genetic alterations are not yet completely elucidated. We aimed to analyze the genetic profile of prolactinomas using a gene panel.

Methods: Next generation sequencing assessing up to 447 genes involved in oncogenesis (OncoPanel) was used to identify single nucleotide variants (SNV) and copy number variations (CNV) of certain target genes. A strict algorithm was followed to prioritize SNV. In statistical analysis, chi-square for categorical and Mann Whitney for continuous variables were used.

Results: Twenty-one subjects (mean age 38 years; 8 men and 13 women) were included in this study. Men were diagnosed with prolactinomas at an older age compared to women (median: 49 vs 30 years, p=0.01). The SF3B1 pathogenic variant was not identified in this cohort. The two-hit model was observed in MEN1 that included a germline inactivation mutation (p.Q447*) (first hit) and MEN1 gene allelic deletion (second hit) in a macroadenoma resistant to dopamine agonist. A BRCA1 germline pathogenic variant (p.E23Vfs*17) was detected in a recurrent macroadenoma with a high MIB-1 proliferation index (≥ 5%). High CNV was observed in adenoma samples (median 46), with prolactinomas from men having significantly higher copy number changes compared to women (median: 68.5 vs 28.0, p=0.04). Chromosome 11p loss and/or chromosome 9 gain were identified in 33.3% of prolactinomas.

Conclusion: In the present study, germline mutations in MEN1 and BRAC1 were identified in prolactinomas. As described in the literature, our sample of prolactinomas had a high number of CNV, especially in men. This genomic disruption may be associated with tumor aggressiveness as most prolactinomas that are surgically resected are resistant to therapy. The recurrent loss of chromosome 11p and gain of chromosome 9 may suggest an association with tumorigenesis.

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P48

Independent Predictors of Remission in the Surgical Treatment of Prolactinomas

Roger Murayi[1], Anira Iqbal[2], Aditya Chauhan[3], Basem Al Achras[4], Pablo F. Recinos[1], Richard Prayson[5], Kevin M. Pantalone[6], Divya Yogi-Morren[6], Pratibha Rao[6], Varun R. Kshettry[1]

[1]Department of Neurological Surgery, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, and Rose Ella Burkhardt Brain Tumor & Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH; [2]Internal Medicine Residency Program, Cleveland Clinic, Cleveland, OH; [3]Internal Medicine Residency Program, The Brooklyn Hospital Center Program, Brooklyn, New York; [4]MedStar Health Internal Medicine Residency Program, Union Memorial Hospital, Baltimore, Maryland; [5]Department of Laboratory Medicine Anatomic Pathology, Cleveland Clinic, Cleveland, OH[6] Department of Endocrinology, Diabetes and Metabolism, Cleveland Clinic, Cleveland, OH

Introduction: Despite being first line therapy, dopamine agonists (DA) are sometimes ineffective or produce intolerable side effects. Surgical resection can lead to high rates of remission in select patients. Many studies investigating patient characteristics that portend remission after surgery do not use statistical models to adjust for covariates and identify independent factors.

Objective: To identify independent predictors of remission after surgical resection of prolactinomas.

Methods: Histopathologically confirmed prolactinomas resected between 2003-2017 at our institution were identified retrospectively. Demographics, preoperative therapies, prolactin levels, Knosp score, tumor characteristics, and outcomes were collected. Independent predictors of surgical remission– defined as normalization of prolactin levels – were assessed in a multivariable logistic regression model using variables identified in an initial bivariate analysis.

Results: 74 patients were identified. The majority were female (46 patients, 62%) and mean age at surgery was 38 years ± 14.1. Mean follow-up time was 49 months. DA therapy was trialed in 54 patients (73%) preoperatively with 15 patients (20%) failing therapy. Surgical remission was achieved in 41 patients (55%) while an additional 12 patients (16%) achieved biochemical control with the addition of DA medications. There was only one recurrence. Remission rate in the macroprolactinoma subset was 81% (21 of 26). In the multivariable logistic regression model, independent predictors of remission were male sex (OR 0.17, p = 0.05), failed medical therapy (OR 0.05, p = 0.001), and diameter (OR 0.89 per mm, p = 0.009).

Conclusion: Surgical resection of prolactinomas offers good remission rates, particularly in certain subsets of patients. Male sex, failed dopamine agonist therapy, and larger size were identified as independent, negative risk factors for achieving remission. Identifying consistent predictors of surgical remission can aid in selecting patients earlier who might be most likely to benefit from surgery.

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REPRODUCTIVE

P49

Study of Functional Hypogonadotropic Hypogonadism in Type 2 Diabetes Mellitus: Its Prevalence, Clinical Correlates, and Cardiovascular Outcomes Compared to Primary Forms

Biagio Cangiano[1,2], Maria Elena Lunati[3], Antonio Conti[2], Elena Galazzi[2], Luca Persani[1,2], Paolo Fiorina[3,4], Marco Bonomi[1,2]

[1]University of Milan, Department of Medical Biotechnology and Translational Medicine, Milan, Italy; [2]Istituto Auxologico Italiano, Department of Endocrinology and Diabetology, Milan, Italy; [3]ASST Fatebenefratelli Sacco, Department of Diabetology and Endocrinology, Milan, Italy; [4]University of Milan, 'L. Sacco' Department of Biomedical and Clinical Sciences, Milan, Italy

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Background: In men with type 2 diabetes mellitus (T2DM) a high prevalence of hypogonadism has been reported, with no consensus on its clinical implications, and whether central or peripheral forms are different. The aim of this observational study is to evaluate: (1) the prevalence of different types of hypogonadism in T2DM; (2) the correlations of gonadal status with severity or duration of diabetes, its complications, therapies, BMI, age and smoking habit; (3) the incidence of major adverse cardiovascular events (MACE) according to the gonadal function.

Patients and Methods: We evaluated data from 106 males, consecutively enrolled in diabetology clinics, aged 18-80; patients with interfering drugs or diseases were excluded. Each patient underwent a complete gonadal axis evaluation and treadmill testing. A 36 months follow up was performed to look for MACEs.

Results: We found evidence of hypogonadism in 49% of T2DM patients: 31% of them having hypogonadotropic forms (HH), and 18% having primary hypogonadism (PH). To logistic regressions PH was associated with higher age (p=0.002) , and creatinine (p=0.02), whereas HH was correlated with BMI (p=0.004) and pack-years (p=0.01). Finally, we found a significant increase in MACEs at 36 months in HH compared to other patients (Fisher, p=0.04).

Conclusions: We found a higher prevalence of HH e PH in T2DM outpatients than previously reported mainly due to high frequency of milder forms (ie, compensated PH and mild HH). We found HH to be associated with smoking habit beyond BMI, and PH with age and creatinine, suggesting different clinical implications for these two forms of hypogonadism. The significantly higher prevalence of three years MACEs in HH, together with its association with smoking, could suggest this condition as an index of cardiovascular disease, and hints at a possible role of gonadal axis function as a cardiovascular predictive factor in T2DM.

The authors have no relevant relationships to disclose.

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Michelle Lundholm

Derya Metin-Armagan

Dennis Nyanyo

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Leili Rahimi

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Ilan Remba-Shapiro

Rashi Sandooja

Sauradeep Sarkar

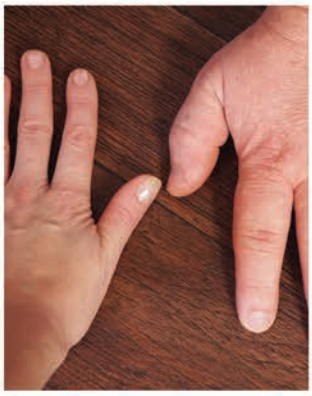
Yuki Shinya

HOPE

FOR THOSE WITH THE GREATEST NEED. AMRYT PHARMA

Amryt is a biopharmaceutical company focused on developing and delivering innovative new treatments to help improve the lives of patients with rare and orphan diseases

Are You Aware of a Patient with Any of These Rare Conditions?

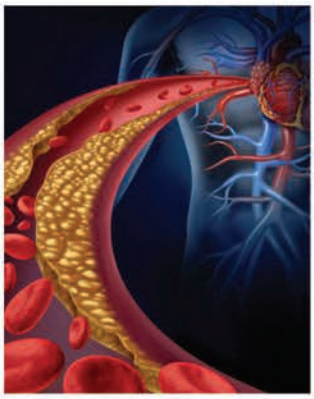


Acromegaly

A life-altering, rare disorder associated with an increased risk of death and reduced quality of life when untreated or poorly controlled.

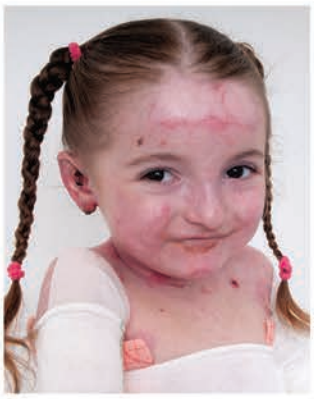
Lipodystrophy

A rare, chronic condition associated with low leptin levels as a result of the loss of adipose tissue.



HoFH

A rare, potentially life-threatening disorder that impairs the body's ability to remove LDL "bad" cholesterol from the blood.



Epidermolysis Bullosa (EB)

A rare, genetic skin disorder characterized by extremely fragile skin that blisters and tears from minor friction or trauma.

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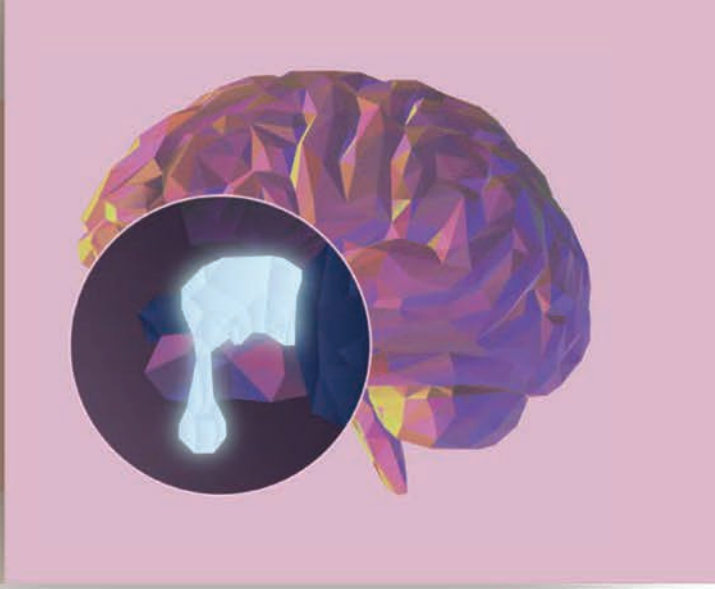
Clinical Challenges of Adult Growth Hormone Deficiency:

A Case-Based Discussion to Improve Patient Outcomes

Wednesday, June 14th | 1:15 - 2:25 PM



PROGRAM OVERVIEW:

Adult growth hormone deficiency (AGHD), a medical condition that results from a lack of growth hormone in adults, has many contributing factors. AGHD symptoms are often vague and non-specific, making clinical diagnosis challenging. To improve patient outcomes, it is essential that healthcare providers understand the significant clinical challenges and identify and diagnose AGHD in a timely manner. Treatment should be individualized based on symptoms, underlying cause and other medical history. Also, patients need education and support to help them adhere to their treatment plan and manage any side effects. At this symposium, experts will review these issues and share best practices for diagnosing, treating, and supporting patients with AGHD.

LEARNING OBJECTIVES:

Upon completion of this educational activity, participants should be able to:

- Describe the comorbidities associated with adult growth hormone deficiency (AGHD)
- Explain how AGHD comorbidities contribute to mortality
- Identify patients who are appropriate candidates for diagnostic screening and recognition of early AGHD
- Summarize AGHD testing protocols
- Review the safety and efficacy of AGHD treatment options
- Explain the ongoing management requirements for AGHD patients

DATE, TIME AND LOCATION:

1:00 – 1:15 CT Light Lunch
1:15 – 2:25 CT Presentation

Westin Michigan Avenue Chicago
Millennium Park Room

WEDNESDAY, JUNE 14 2023

Education program supported by an unrestricted educational grant from Novo Nordisk.

PROGRAM FACULTY:

Program Chair:
Maria Fleseriu, MD, FACE
Professor of Medicine (Endocrinology, Diabetes and Metabolism) and Neurological Surgery
Director, Pituitary Center
Oregon Health & Science University, Portland, USA

Faculty Presenter:
Andrew R. Hoffman, MD
Professor of Medicine, Endocrinology
Stanford Medical Center, Stanford, USA

Faculty Presenter:
Gudmundur Johannsson, MD, PhD
Professor of Endocrinology
Deputy Director, Institute of Medicine
Sahlgrenska Academy, University of Gothenburg, Sweden

Faculty Presenter:
Julie Silverstein, MD
Medical Director, Pituitary Center
Associate Professor of Medicine and Neurological Surgery
Division of Endocrinology, Metabolism and Lipid Research
Washington University School of Medicine
St. Louis, USA

PROGRAM AGENDA:

1:15 – 1:25	Introductions, Overview and Pre-Event Polling Questions **– Maria Fleseriu, MD, FACE**
1:25 – 1:40	Diagnosis and Who to Test for Adult Growth Hormone Deficiency **– Julie Silverstein, MD**
1:40 – 2:00	Available GH Replacement Therapies, Efficacy and Safety **– Gudmundur Johannsson, MD, PhD**
2:00 – 2:15	Monitoring and Ongoing Management of Adult Growth Hormone Deficiency **– Andrew R. Hoffman, MD**
2:15 – 2:25	Post-Event Polling Questions, Open Discussion and Audience Questions **– Faculty Panel**

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education ACCME) through the joint providership of Your CE Source and CMM Global. Your CE Source is accredited by the ACCME to provide continuing medical education for physicians. Your CE Source designates this live activity for a maximum of *1.5 AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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