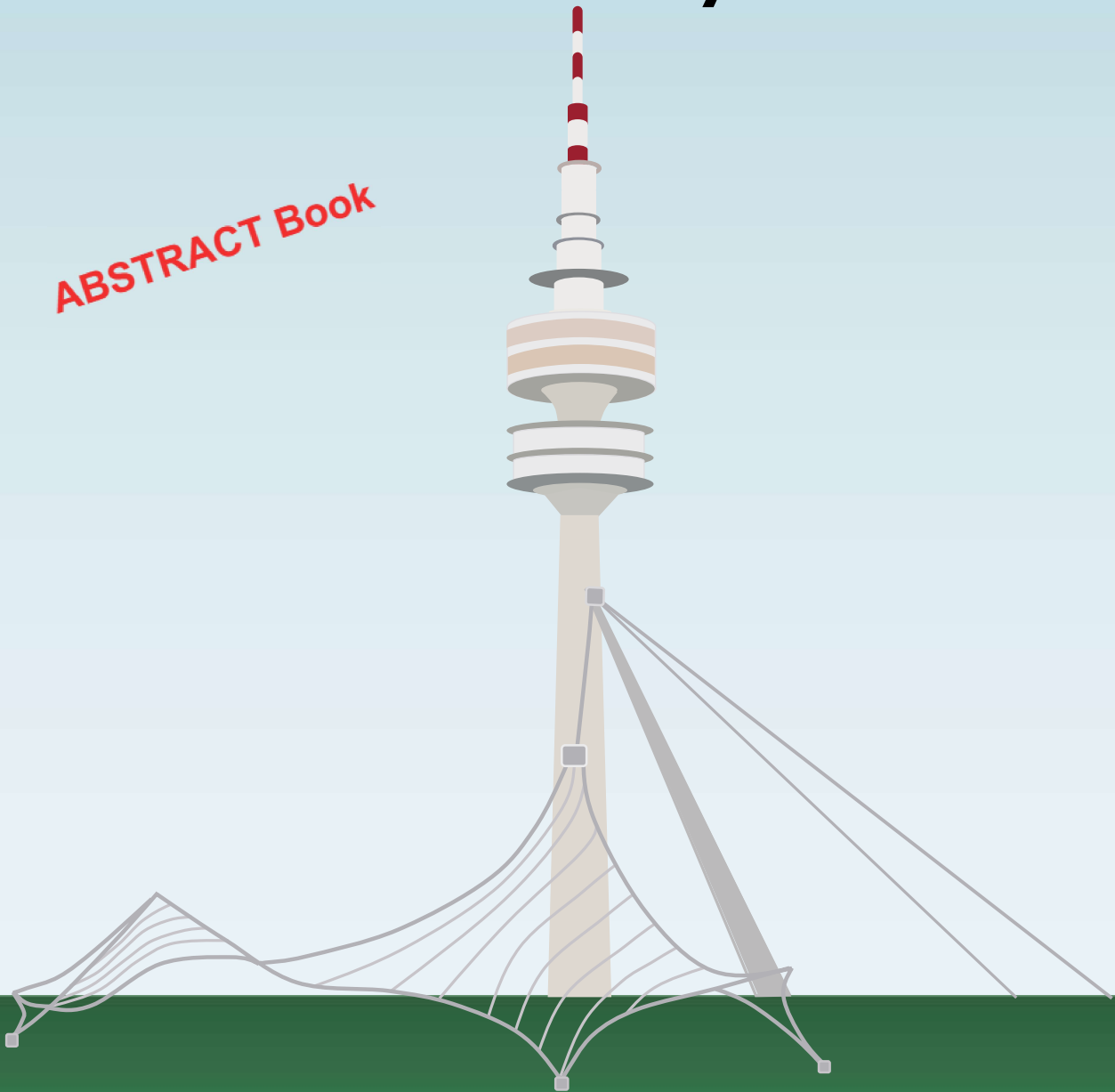


8. ENEA Workshop on Precision Pituitary Medicine

ABSTRACT Book



December 7-9, 2023 | Munich, Germany

A meeting of the



Friday, 08th December 2023

ORAL COMMUNICATIONS
Abstract-ID: 32**ENDOGENOUS CUSHING'S SYNDROME IS ASSOCIATED WITH INCREASED CANCER RISK: A NATIONWIDE ISRAELI COHORT STUDY**Yaron Rudman¹, Hiba Masri-Iraqi¹, Liat Sasson¹, Tzippy Shohat², Shiri Kushnir³, Ilan Shimon⁴, Amit Akirov⁵¹Beilinson Hospital, Rabin Medical Center, Institute of Endocrinology, Petah Tikva, Israel²Rabin Medical Center Beilinson Hospital, Israel³Beilinson Hospital, Rabin Medical Center, Research Authority, Petah Tikva, Israel⁴Rabin Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Petah-Tiqva, Israel⁵Rabin Medical Center, Beilinson Campus, Petah-Tikva, IsraelBackground

There are no clear data on the association between Cushing's syndrome (CS) and cancer risk. We aimed to assess the risk of cancer in CS patients, compared with matched controls.

Methods

We conducted a nationwide retrospective cohort study of patients with endogenous CS diagnosed during 2000–2023, using the electronic health record database of Clalit Health Services, Israel. All patients had an ICD-10 diagnosis of CS and biochemical evidence of hypercortisolism and were classified according to disease source as pituitary CS, cortisol-secreting adrenal adenoma, or indeterminate source. Patients with adrenal cancer or ectopic CS were excluded. Patients with CS were individually matched in a 1:5 ratio according to age, sex, socioeconomic status, and body-mass index.

The primary outcome was first diagnosis of any malignancy following CS diagnosis, calculated using the Fine and Gray hazards model with death as a competing event. The risk for malignancy was also assessed according to remission status within two years of diagnosis.

Results

The study cohort included 609 CS patients and 3018 matched controls [mean age at diagnosis, 48.0±17.2; 2371 (65.4%) women]. Of these, 251 (41.2%) patients had pituitary CS, 200 (32.8%) patients had adrenal CS, and in 158 (25.9%) cases the source was indetermined. At baseline, 50 (8.2%) CS patients and 117 (3.9%) controls had a history of prior malignancy ($p<0.05$), mainly due to malignancies diagnosed within 5 years of CS diagnosis (5.9% vs. 2.2%, $p<0.05$), while there was no difference in the rate of malignancies diagnosed more than 5 years prior to CS diagnosis (2.3% vs. 1.7%, $p=0.32$).

During follow-up [median, 14.7 years (IQR 9.9–20.2)], the risk for cancer was higher for CS patients compared with their matched controls (hazard ratio [HR], 1.78, 95% CI 1.44-2.20, $p<0.01$). The risk for malignancy was elevated in patients with pituitary CS (HR 1.65, 95% CI 1.15-2.36, $p<0.01$) and in patients with adrenal CS (HR 2.36, 95% CI 1.70-3.29, $p<0.01$). The risk for malignancy was higher among patients with pituitary CS who did not achieve early remission ($n=69$) compared with those in remission ($n=99$) [unadjusted HR 3.89 (95% CI 1.41-10.75, $p=0.01$)]. The unadjusted HR in patients with adrenal CS who did not achieve early remission ($n=39$) compared with those in remission ($n=113$) was 1.68 (95% CI 0.83-3.40, $p=0.17$).

Conclusion

Endogenous Cushing's syndrome is associated with increased cancer risk. Our data suggest that early biochemical remission, particularly in patients with pituitary CS, may attenuate this risk.

Abstract-ID: 94

E-CADHERIN DOWNREGULATION MAY CONTRIBUTE TO INCREASED PROLIFERATION, AGGRESSIVENESS AND REFRACTORINESS IN PITUITARY NEUROENDOCRINE TUMORS

Fábio Reis¹, Micaella Miranda², Rita Joaquim², Catarina Miranda², Tiago Oliveira³, Dolores López-Presa³, Cláudia Faria⁴, Isidro Cortes-Ciriano⁵, Márta Korbonits⁶, Maria-João Bugalho⁷, Ana Luísa Silva⁸, Pedro Marques⁹

¹*Instituto de Saúde Ambiental Da Faculdade de Medicina Da Universidade de Lisboa (Isamb), Lisboa, Portugal*

²*Instituto de Saúde Ambiental Da Faculdade de Medicina Da Universidade de Lisboa (Isamb), Lisbon, Portugal*

³*Pathology Department, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (Chuln), Lisbon, Portugal*

⁴*Neurosurgery Department, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (Chuln), Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina Da Universidade de Lisboa, Lisbon, Portugal*

⁵*European Molecular Biology Laboratory, European Bioinformatics Institute, Wellcome Genome Campus,, Hinxton, United Kingdom*

⁶*Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom*

⁷*Endocrinology Department, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (Chuln), Faculty of Medicine, Lisbon University, Lisbon, Portugal*

⁸*Faculdade de Medicina Da Universidade de Lisboa, Faculty of Medicine, Lisbon University, Laboratório de Genética, Lisbon, Portugal*

⁹*Pituitary Tumor Unit, Endocrinology Department, Hospital Cuf Descobertas, Faculdade de Medicina, Universidade Católica Portuguesa, Lisbon, Portugal*

Introduction: Epithelial-to-mesenchymal transition (EMT) is a process by which epithelial cells lose their polarity and gain migratory abilities, resulting in increased invasiveness, aggressiveness and resistance to treatment. EMT hallmark is the loss of E-cadherin. EMT remains largely unexplored in pituitary neuroendocrine tumors (PitNETs). We aimed to study the EMT in PitNETs, particularly the relevance and pattern of E-cadherin expression in determining the clinical phenotype and outcomes of PitNET patients.

Methods: The expression of *CDH1* (encodes E-cadherin) and *ZEB1* (mesenchymal marker) was studied by RT-qPCR on 86 PitNETs from patients who underwent surgery at our center between 2014-2020: 62 nonfunctioning-PitNETs (NF-PitNETs), 18 somatotroph tumors and 6 corticotroph tumors. E-cadherin immunostaining was performed and analyzed on the basis of its location relative to the cytoplasmic membrane, and reported as percentage (%) of complete, incomplete or absent E-cadherin membranous staining, as well as using a semi-quantitative E-cadherin score based on expression pattern (ranging from 0 if no E-cadherin expression, up to 4 if all tumor cells had complete cytoplasmic membrane staining).

Results: In our cohort, 47.7% were males, age at diagnosis was 56±15yr (mean±SD), and mean follow-up was 6±4yr. E-cadherin score and %cells with complete membranous E-cadherin staining correlated positively with *CDH1* mRNA levels. *CDH1* and *ZEB1* mRNA expression did not differ among PitNET subtypes, but acromegaly and Cushing's disease patients had higher rates of absent membranous E-cadherin. *CDH1* expression was lower in patients who presented with pituitary apoplexy, and in those who had a Ki-67>3%, and tended to be lower in patients who more often required multimodal and multiple treatments. *CDH1* mRNA levels correlated negatively with total number of treatments and surgeries. There were no correlations between *ZEB1* expression and clinico-outcome parameters. Most PitNETs expressed E-cadherin in the cytoplasmic membrane (87.2%). Lower mean E-cadherin score were found in males, patients who had headache at diagnosis, and a higher %cells lacking membranous E-cadherin were also found in patients who had pituitary apoplexy. Lack of E-cadherin expression was associated with higher Ki-67 and with need for post-operative medical therapy, and PitNETs with suprasellar extension had lower rates of complete E-cadherin membranous staining.

Conclusions: Our data suggest that EMT activation in PitNETs, reflected by E-cadherin downregulation, may contribute to an increased tumor proliferation and aggressiveness, as well as to more refractory and difficult-to-treat disease.

Abstract-ID: 101

PREDICTIVE FACTORS FOR HYPERGLYCAEMIA DURING PASIREOTIDE TREATMENT: A POST HOC ANALYSIS OF THE PHASE IV B2219 STUDY

Ulla Feldt-Rasmussen¹, Marek Bolanowski², Shao-Ling Zhang³, Yerong Yu⁴, Przemysław Witek⁵, Pramila Kalra⁶, Noppadol Kietsiroje⁷, Andrea Piacentini⁸, Alberto Pedroncelli⁹, Susan Samson¹⁰

¹Copenhagen University Hospital, Rigshospitalet, Dept of Endocrinology, Pe 2132, Copenhagen, Denmark

²Department of Endocrinology, Diabetes and Isotope Therapy, Wrocław Medical University, Wrocław, Poland

³Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China

⁴West China Hospital of Sichuan University, Department of Endocrinology and Metabolism, Chengdu, China

⁵Endocrinology and Diabetes, Medical University of Warsaw, Department of Internal Medicine, Warsaw, Poland

⁶Department of Endocrinology and Metabolism, Ms Ramaiah Medical College and Hospitals, Bengaluru, India

⁷Faculty of Medicine, Prince of Songkla University, Endocrinology and Metabolism Unit, Internal Medicine Department, Songkhla, Thailand

⁸Recordati Spa, Milan, Italy

⁹Camurus, *, Sweden

¹⁰Mayo Clinic, Departments of Medicine and Neurologic Surgery, Jacksonville, United States

Introduction: Pasireotide efficacy and safety in people with acromegaly or Cushing's disease (CD) is confirmed in a comprehensive clinical trial programme. Pasireotide-induced hyperglycaemia, expected based on the drug's mechanism of action, is manageable with low rates of treatment discontinuation. A prospective, randomised Phase IV study (B2219, NCT02060383) was designed to advance knowledge of pasireotide-induced hyperglycaemia management. This *post hoc* analysis assessed factors that might predict development of pasireotide-induced hyperglycaemia.

Methods: In B2219, participants (Pts) with acromegaly or CD who did not need therapy for hyperglycaemia, or were managed with metformin alone, entered the non-randomised observational arm. Pts who developed hyperglycaemia not managed with metformin alone were randomised to incretin-based therapy or insulin. Pts were evaluated based on whether therapy for hyperglycaemia during pasireotide treatment was needed. Logistic regression analyses evaluated quantitative and qualitative predictive factors for pasireotide-induced hyperglycaemia.

Results: Of 190 Pts with acromegaly and 59 with CD, 88 (46.3%) and 15 (25.4%), respectively, did not need antihyperglycaemic medication during pasireotide treatment; Pt characteristics were similar across subgroups at baseline (BL). Most Pts who did not develop hyperglycaemia had a mean age of <40 years (acromegaly 62.5%, CD 86.7%), BL glycated haemoglobin (HbA_{1c}) <48 mmol/mol (6.5%) (acromegaly 98.9%, CD 100.0%) and BL fasting plasma glucose (FPG) <5.5 mmol/L (<100 mg/dL) (acromegaly 76.1%, CD 100.0%). Age (odds ratio [OR] 1.04, 95% CI 1.0–1.1), BL HbA_{1c} (OR 3.53, 95% CI 1.3–9.9) and prediabetes or diabetes conditions (OR 3.03, 95% CI 1.2–7.6) were identified as risk factors for pasireotide-induced hyperglycaemia in Pts with acromegaly. BL FPG (OR 1.16, 95% CI 1.0–1.3) was associated with increased risk of pasireotide-induced hyperglycaemia in Pts with CD. Overall, investigator-reported adverse events (AEs) of hyperglycaemia and diabetes mellitus occurred in 21.1% and 14.2% of Pts with acromegaly and 28.8% and 11.9% of Pts with CD, respectively. More Pts with diabetes or prediabetes conditions at BL had hyperglycaemia-related AEs than Pts with normal glucose levels. Hyperglycaemia-related AEs were managed with antihyperglycaemic medication (acromegaly 26.3%, CD 30.5%); few Pts temporarily stopped treatment (acromegaly 3.7%, CD 10.2%).

Conclusions: These data suggest that age, HbA_{1c}, FPG and prediabetes or diabetes conditions at BL are associated with increased risk of developing pasireotide-induced hyperglycaemia. AEs were mostly manageable with metformin, followed by incretin-based therapy if needed, and most Pts could continue pasireotide treatment; dietary modification, exercise and education are also important. Potential risk factors for pasireotide-induced hyperglycaemia may help identify Pts who need close monitoring to ensure optimal treatment outcomes with pasireotide.

Abstract-ID: 103

OSILODROSTAT SHOWED HIGH EFFICACY IN 210 PATIENTS WITH CUSHING'S DISEASE IN PHASE III LINC 3 AND LINC 4 STUDIES: A POST HOC ANALYSIS COMPARING PATIENTS OF ASIAN AND NON-ASIAN ORIGIN

Maria Fleseriu¹, Beverly Biller², Rosario Pivonello³, Eun Jig Lee⁴, Rattana Leelawattana⁵, Jung Hee Kim⁶, Rama Walia⁷, Yerong Yu⁸, Zhihong Liao⁹, Peter Snyder¹⁰, Andrea Piacentini¹¹, Alberto Pedroncelli¹², AKIRA SHIMATSU¹³

¹Northwest Pituitary Center, Ohsu, Department of Medicine, Department of Neurological Surgery, Portland, United States

²Massachusetts General Hospital, Neuroendocrine and Pituitary Tumor Clinical Center, Boston, United States

³Sezione DI Endocrinologia, Università Federico II DI Napoli, Naples, Italy

⁴Yonsei University College of Medicine, Department of Internal Medicine, Seoul, Korea, Rep. of South

⁵Prince of Songkla University, Songkhla, Thailand

⁶Department of Internal Medicine, Division of Endocrinology and Metabo, Seoul, Korea, Rep. of South

⁷Postgraduate Institute of Medical Education and Research (Pgimer), Department of Endocrinology, Chandigarh, India

⁸West China Hospital of Sichuan University, Department of Endocrinology and Metabolism, Chengdu, China

⁹Sun Yat-Sen University, Guangzhou, China

¹⁰Perelman School of Medicine, University of Pennsylvania, Philadelphia, United States

¹¹Recordati Spa, Milan, Italy

¹²Camurus, *, Sweden

¹³Advanced Medical Care Center, Social Medical Corporation Seikoukai, Kusatsu-Shi, Japan

Introduction: Osilodrostat, a potent oral 11 β -hydroxylase inhibitor, provided rapid, sustained cortisol normalisation in patients (pts) with Cushing's disease (CD) in two Phase III studies (LINC3, NCT02180217; LINC4, NCT02697734). This pooled LINC3 and LINC4 analysis evaluated osilodrostat efficacy and safety in pts of Asian and non-Asian origin with CD.

Methods: LINC3 and LINC4 data were pooled. LINC3 comprised a 48-week (W) core phase, including an 8W randomised withdrawal for eligible pts. LINC4 included an upfront 12W, double-blind, randomised, placebo-controlled period and 36W of open-label osilodrostat. Both studies had an optional extension. Here, efficacy and safety outcomes for pts of Asian and non-Asian origin were evaluated separately, excluding periods during which pts received placebo.

Results: 56/210 pts (27%) were of Asian origin, enrolled in China (n=16), Republic of Korea (n=14), Japan (n=9), Thailand (n=9), India (n=7) and USA (n=1). Most non-Asian pts were Caucasian (n=138/154; 90%). Relative osilodrostat bioavailability was approximately 20% higher in pts of Asian origin than other ethnicities; body weight was not a major determinant of this difference. Median (min–max) osilodrostat dose in Asian and non-Asian pts respectively was 3.8mg (1–25) and 7.3mg (1–47). Mean urinary free cortisol (mUFC) control was achieved at W48 and W72 in 64.3% and 68.1% of Asian and 68.2% and 75.8% of non-Asian pts, respectively. At W48 and W72, 47.2% and 58.1% of Asian pts and 43.3% and 45.0% of non-Asian pts had control of both mUFC and late-night salivary cortisol. Similar improvements from baseline in cardiovascular and metabolic-related parameters and physical manifestations of hypercortisolism were observed in both groups during osilodrostat treatment. The most common investigator-reported adverse events (AE) in Asian pts were adrenal insufficiency (44.6%), nausea (33.9%), and decreased appetite (26.8%), and in non-Asian pts, nausea (45.5%), fatigue (40.9%) and headache (39.0%). The most common serious AE in Asian and non-Asian pts was adrenal insufficiency (5.4% and 5.2%). Hypocortisolism-related AEs occurred in 58.9% and 40.3% of Asian and non-Asian pts, respectively, commonly reported by investigators as adrenal insufficiency (44.6% and 22.1%). Pituitary tumour enlargement-related AEs occurred in 21.4% of Asian and 9.1% of non-Asian pts. Arrhythmogenic potential and QT prolongation-related AEs were infrequent in all pts.

Conclusions: The beneficial effects of osilodrostat were similar across both groups for mUFC control, improvements in cardiovascular and metabolic-related parameters, and physical manifestations of hypercortisolism. The median dose required to achieve mUFC control was lower in Asian pts than non-Asian pts. Although hypocortisolism-related and pituitary tumour enlargement-related AEs were reported more frequently in Asian pts than non-Asian pts, osilodrostat was generally well tolerated in both groups.

Abstract-ID: 117

SOMATOTROPH PITNETS POSITIVE FOR NR5A1 (SF-1) EXPRESSION REPRESENT ONE OF THE MOLECULAR SUBTYPES OF TUMORS CAUSING ACROMEGALY.

Mateusz Bujko¹, Julia Rymuza², Paulina Kober³, Beata Mossakowska¹, Natalia Rusetska¹, Maria Maksymowicz¹, Aleksandra Nyc¹, Szymon Baluszek¹, Grzegorz Zieliński⁴, Jacek Kunicki¹, Mateusz Bujko⁵

¹*Maria Skłodowska-Curie National Research Institute of Oncology, 02-781 Warsaw, Poland*

²*Maria Skłodowska-Curie National Research Institute of Oncology, 02-781 Warsaw, Poland., Poland*

³*Maria Skłodowska-Curie National Research Institute of Oncology, 02-781 Warsaw, Poland.*

⁴*Military Institute of Medicine, 04-141 Warsaw, Poland*

⁵*Maria Skłodowska-Curie National Research Institute of Oncology, Department of Molecular and Translational Endocrinology, Warsaw, Poland*

Somatotroph pituitary neuroendocrine tumors (PitNETs) commonly cause acromegaly, which is a hormonal disorder resulting from excessive growth hormone secretion. They represent histologically heterogeneous group of tumors.

We applied molecular profiling methods including RNA sequencing as well as oligonucleotide microarrays dedicated to DNA methylation (EPIC arrays, Illumina) and cytogenetic (CytoSNP850K, Illumina) analysis to characterize 48 somatotroph PitNETs.

The results show that somatotroph pituitary tumors fall into 3 molecular categories, characterized by distinct gene expression profiles, different DNA methylation pattern and distinct level of DNA copy number abnormalities.

One of the subtypes is characterized by specific high expression of the NR5A1 gene encoding steroidogenic factor-1 (SF-1) transcription factor. Although SF-1 is considered as a marker of gonadotroph pituitary cells its expression in some of somatotroph PitNETs was previously shown in independent literature reports.

Our results indicate that somatotroph PitNETs positive for NR5A1 expression are a group of histologically densely granulated, GNAS-mutation negative ones. Specific gene expression profile of this tumor subtype includes high expression of GIPR that is thought to cause paradoxical increase in the level of GH secreted by some of somatotroph tumors after glucose intake. NR5A1 positive tumors have also high expression of steroidogenesis-related genes such as STAR and CYP11A1 that are known to be induced by SF-1.

These tumors have distinct DNA methylation profile with global genomic hypomethylation which is most pronounced at gene promoter regions. Low DNA methylation levels of key regulatory elements of NR5A1 and GIPR correlate with high expression of these genes in NR5A1-positive somatotroph PitNETs. Interestingly, these tumors have also the highest number of cytogenetic abnormalities (mainly genomic amplifications) which is strikingly different as compared to a subtype of sparsely granulated somatotroph PitNETs with relatively stable genomes that form another molecular subtype.

Abstract-ID: 172

SERUM SOLUBLE ALPHA KLOTHO, A NEW AND STABLE BIOMARKER OF GROWTH HORMONE ACTION

Júnia Ribeiro de Oliveira Longo Schweizer¹, Katharina Schilbach², Michael Haenelt³, Anica Pauline Gagliardo⁴, Annette Peters⁵, Barbara Thorand⁶, Martin Bidlingmaier⁷

¹LMU Klinikum; Med. Klinik und Poliklinik IV / Endokrinologie; Med. Klinik und Poliklinik IV, Endokrinologisches Labor, Innenstadt, Munich, Germany

²Med. Klinik & Poliklinik IV, LMU Klinikum, Medizinische Klinik und Poliklinik IV, München, Germany

³Klinikum der Universität München, Medizinische Klinik und Poliklinik IV, Ludwig Maximilians Universität München; Med. Klinik und Poliklinik IV / Endokrinologie; Medizinische Klinik und Poliklinik IV, Munich, Germany, München, Germany

⁴Medizinische Klinik und Poliklinik IV, LMU Klinikum München, Endokrinologisches Labor, München, Germany

⁵Epidemiologie Medizinische Fakultät, LMU München, Helmholtz Zentrum München – Deutsches Forschungszentrum für Gesundheit und Umwelt, Germany

⁶Helmholtz Zentrum München, GmbH Deutsches Forschungszentrum für Gesundheit und Umwelt, Germany

⁷LMU Klinikum, Med. Klinik und Poliklinik IV / Endokrinologie, Med. Klinik und Poliklinik IV, Munich, Germany

Background: Alpha Klotho is a transmembrane protein. Its soluble portion can be secreted and measured in serum (soluble alpha klotho ($s\alpha$ KL)). $s\alpha$ KL has been related to the growth hormone axis, as $s\alpha$ KL concentrations are very high in active acromegaly, and significantly reduces after disease control. Therefore $s\alpha$ KL is suggested as a new biomarker for growth hormone (GH) excess. However, little is known about the impact of biological variables other than GH. **Methods:** Serum $s\alpha$ KL (pg/mL) was measured by ELISA (IBL, Hamburg, Germany). We first evaluated pre-analytical stability, defined a reference interval for $s\alpha$ KL in healthy subjects (A: n=890), and compared the concentrations to those in patients with non-functional pituitary tumors (NFPA, B, n=18) or prolactinomas (C, n=66). Moreover, we evaluated the potential impact of various biological variables on $s\alpha$ KL. **Results:** The assay for $s\alpha$ KL exhibits excellent intra/inter-assay CVs (<10%) and linearity (92-107%). Concentrations were not significantly affected by storage at room temperature for 72 hours, or by up to 4 freeze/thaw cycles (recovery>90%). $s\alpha$ KL concentrations did not significantly differ between serum and EDTA samples ($p>0.05$). The reference interval (2.5-97.5%) for $s\alpha$ KL is 152-1303 (A: median: 673(IQR: 543-846)). $s\alpha$ KL was not different in NFPA ($p>0.05$), but higher in prolactinoma (902(754-1228); A vs.C, $p<0.0001$). Compared to IGF-I and IGFBP 3, $s\alpha$ KL exhibited a weaker negative correlation with age, (body mass index (BMI), waist-hip-ratio and cholesterol ($r_s=-0.30, -0.13, -0.12, -0.16$, respectively, $p<0.05$ for all). In contrast, a positive correlation was seen with glomerular filtration rate and IGF-I ($r_s=0.11, 0.31$, respectively, $p<0.001$ for all). While IGF-I and IGFBP 3 correlated with fasting glucose, $s\alpha$ KL did not ($p>0.05$), and did not vary significantly during oral glucose tolerance test (n=10, $p>0.05$). Slight reductions in $s\alpha$ KL were observed females on estrogen monotherapy ($p<0.05$). There was no correlation between $s\alpha$ KL and calcium metabolism. **Conclusion:** We established a reference range for $s\alpha$ KL, a highly stable biomarker of GH action. It is less affected by many biological variables than IGF-I and IGFBP 3. However, our data suggest it decreases in conditions of hepatic GH-resistance (oral estrogen), and is slightly increased by prolactin, most likely due to its somatotrophic activity. The regulation of $s\alpha$ KL shedding might not be impacted by calcium metabolism.

Friday, 08th December 2023

EYRC ORAL COMMUNICATIONS**Abstract-ID: 45****COPEPTIN AND OXYTOCIN IN MDMA-INDUCED HYPONATREMIA: A POOLED ANALYSIS OF FOUR PLACEBO-CONTROLLED CROSS-OVER TRIALS**Cihan Atila¹, Isabelle Straumann², Patrick Vizeli², Friederike Holze², Matthias Liechti³, Mirjam Christ-Crain⁴¹University Hospital Basel, 1 Department of Endocrinology, Diabetology and Metabolism, University Hospital Basel, Basel, Switzerland; ² Department of Clinical Research, University of Basel, Basel, Switzerland; ³ Department of Endocrinology, Diabetology and Metabolism, Basel, Switzerland²University Hospital Basel³University Hospital Basel, Switzerland⁴University Hospital Basel, Department of Clinical Research, University of Basel, Basel, Switzerland, Department of Endocrinology, Diabetology and Metabolism, University Hospital Basel, Basel, Switzerland, Basel, Switzerland

BACKGROUND 3,4-Methylenedioxymethamphetamine (MDMA) is a trending recreational drug but also has potential to enter clinical practice for treating posttraumatic stress disorder. There have been multiple reports of acute hyponatremia, a serious complication arising from ingesting even a single dose of MDMA. The assumed mechanisms for the aetiology of hyponatremia are an increased vasopressin release inducing the syndrome of inappropriate anti-diuresis, combined with increased thirst causing water intoxication. However, data on prevalence and severity of hyponatremia, the underlying mechanisms of action, and the potential effect of fluid restriction on lowering the risk of hyponatremia are limited to smaller case series or unavailable.

METHODS Pooled analysis of four single-centre placebo-controlled cross-over trials, including 96 healthy controls (median age 27y [IQR 26 to 29]; 35% females) at the University Hospital Basel, Switzerland. Participants were assigned to a single oral dose of MDMA (100 or 125 mg) or placebo first, with a wash-out period of at least 10 days between both experimental sessions. Plasma oxytocin, copeptin (a surrogate marker of vasopressin), and sodium were measured repeatedly within 300 minutes after drug intake. In three of the four analysed studies, there were no fluid restrictions, while in one study, fluid intake was controlled.

FINDINGS At baseline, the median plasma sodium level was 140 mmol/l [138 to 142] and decreased in response to MDMA by 4 mmol/l [-5 to -3], leading to hyponatremia in 31 % of the participants. Among hyponatraemic participants, the minimum plasma sodium level was 133 mmol [132-134]. In participants performing fluid restriction, no hyponatremia (n=0/15) occurred during the experimental session, while in those not limited to fluid intake, the prevalence of hyponatremia was 41% (n=33/81), suggesting that fluid restriction significantly prevented hyponatremia (p=0.002). The median plasma oxytocin at baseline was 77 pg/ml [59 to 104] and increased by 417 pg/ml [224 to 772] in response to MDMA, while plasma copeptin was 3.9 pmol/l [2.6 to 5.7] and only slightly increased by 0.3 pmol/l [-0.7 to 1.5]. The decrease in plasma sodium levels was significantly correlated with the increase in oxytocin (r= -0.41; p<0.001), while no correlation was observed between the change in plasma sodium and copeptin (r= -0.13; p=0.22).

INTERPRETATION We report a high prevalence of acute and mainly mild hyponatremia in response to MDMA, which can effectively be prevented by fluid restriction. Hyponatremia is associated with acute strong oxytocin but not copeptin release - this challenges the current hypothesis of direct vasopressin release and rather indicates that the increase in oxytocin mimics the effect of vasopressin in the kidneys due to close structural homology.

Abstract-ID: 188

DISTURBED ER PROTEIN PROCESSING IMPACTS ACTH PRODUCTION IN FUNCTIONING CORTICOTROPH ADENOMAS

Merisa Abusdal¹, Maria E. Walewska², Hemaseh Bideli³, Kjersti R. Normann², Tuula A. Nyman⁴, Jens Bollerslev², Jens P. Berg⁵, Nicoleta C. Olarescu⁶

¹*Section of Specialized Endocrinology, Oslo University Hospital (Ous) Oslo and University of Oslo, Department of Endocrinology, Oslo, Norway*

²*Section of Specialized Endocrinology, Department of Endocrinology, Oslo University Hospital (Ous) Oslo, Norway*

³*Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Norway*

⁴*Department of Immunology, Ous and University of Oslo, Oslo, Norway*

⁵*Department of Medical Biochemistry, Ous, Oslo and University of Oslo, Norway*

⁶*Section of Specialized Endocrinology, Department of Endocrinology, Oslo University Hospital (Ous), Oslo, and University of Oslo, Oslo, Norway*

Objective

Adrenocorticotrophic hormone (ACTH) secreted from functioning pituitary adenomas (FCA) leads to Cushing's disease. FCA are generally microadenomas whereas the silent (SCA) counterpart, are mostly macroadenoma with extrasellar expansion. The expression of genes involved in endoplasmic reticulum (ER) protein processing activity were upregulated in FCA, when compared to SCA, as recently shown (1). We hypothesized that the inhibition of molecules involved in protein processing in the ER, which induces ER stress and unfolded protein response (UPR), reduces ACTH production and secretion.

Methods

Clinical and MRI characteristics were recorded in a cohort of 51 patients (34 FCA and 17 SCA). The expression of selected genes involved in ER protein processing and proopiomelanocortin (POMC) synthesis was measured by real-time quantitative PCR (RT-qPCR) in adenoma tissue. Mouse pituitary corticotroph tumor (AtT-20) cells and human primary cells isolated from FCA were treated with thapsigargin (Tg, a Ca²⁺-ATPase inhibitor), and NECA (a specific Grp94 inhibitor), to induce ER stress, followed by gene and protein analyses, and measurement of ACTH production and secretion in the cell media.

Results

FCA expressed higher levels of ER protein processing genes (CALR, PDIA3, GRP78, GRP94, RNP1, HSPH1, CRYAB and UGGT2) as compared to SCA ($p < 0.05$, for all).

POMC expression was first upregulated at 6 hr ($p = 0.003$) and then downregulated at 24 hr by NECA ($p = 0.0009$), whereas Tg downregulated POMC at both time points in AtT-20 cells ($p < 0.0001$, for both). Gene and protein expression of molecules involved in ER protein processing, including CALR, GRP78, GRP94, and UGGT1 were significantly upregulated by Tg at 24 hr in AtT-20 cells.

Secreted ACTH was decreased by 23% in AtT-20 cells and 40% in primary cells by Tg treatment at 24 hr ($p < 0.05$). Intracellular ACTH level was significantly reduced 23% by NECA, but not Tg, in AtT-20 cells.

Conclusion

ER protein processing genes are higher expressed in FCA than SCA, and induction of ER stress inhibits ACTH secretion. FCAs depend on a well-functioning and high-capacity ER in order to secrete ACTH, a process that could probably be exploited as a target for medical treatment.

References

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Abstract-ID: 205

EFFECTS OF GLP-1-RECEPTOR AGONISTS ON COPEPTIN IN HEALTHY VOLUNTEERS AND PATIENTS WITH PRIMARY POLYDIPSIA

Svenja Leibnitz¹, Mirjam Christ-Crain¹, Bettina Winzeler¹

¹University Hospital of Basel, Endocrinology, Diabetes and Metabolism, Basel, Switzerland

Background/Introduction:

Today, GLP-1 receptor agonists have great clinical importance in the treatment of type 2 diabetes and obesity. Beside their known mechanisms to lower blood sugar, enhance satiety signals and reduce appetite, GLP-1 also seems to play a significant role in sodium and water balance. This can be supported by the finding of GLP-1 receptor expression in various locations of the kidney, the enteric system and key brain structures.

Recent findings investigating long-term effects of treatment with GLP-1 receptor agonists showed a significant reduction of fluid intake and 24-h-urine volume compared to placebo. There were no changes in serum sodium, urinary sodium excretion or in hormones of the RAAS system as a possible physiological explanation.

To our knowledge data are inconclusive regarding physiological mechanisms that could explain these observations. Furthermore, no direct effect of GLP-1 on Vasopressin has been observed to date.

The aim of this secondary analysis was to investigate changes of Copeptin levels in euvoletic participants treated with dulaglutide versus placebo. We hypothesize that dulaglutide effects a stimulation in Vasopressin due to reduced water intake, lowered blood pressure and nausea which are known side effects of GLP-1 receptor agonists.

Methods:

A secondary analysis of randomized, double-blind, placebo-controlled, crossover-trials in 20 healthy participants (GATE trial) and 34 patients with primary polydipsia (GOLD trial) was performed at the University Hospital of Basel between 2016 and 2019. In both studies participants received either Dulaglutide (Trulicity®) 1.5 mg or placebo, in random order, subcutaneously once weekly over a three-week treatment phase and attended an 8-hour evaluation visit during the last treatment week. After a wash-out period of at least three weeks, patients received the complementary intervention.

Results:

All 54 participants of the two cross-over trials were included. Median age was 27 (IQR 24 to 37) years and 63% were female. Median plasma sodium concentration, plasma osmolality and GFR were all in the mid-normal range. To estimate the treatment effect of Dulaglutide, we derived the absolute within-subject differences of Copeptin after a three-week treatment phase between Dulaglutide and placebo and used the wilcoxon rank test for statistical analysis. After a three-week treatment phase, Dulaglutide showed a significant suppression of Copeptin in both trials ($p=0.04$) compared to placebo [GOLD: treatment effect: -0.67pmol/L versus GATE: treatment effect: -1pmol/L].

Conclusion:

This analysis will provide further information on the direct effects of GLP1 on Vasopressin and reveal physiological mechanisms that explain the role of GLP-1 in sodium and water balance.

Abstract-ID: 208

DUE TO BODY IMAGE CONCERNS SOCIAL MEDIA USING HABITS ARE ALTERED IN PATIENTS WITH ACROMEGALY

selin tekin¹, süleyman sendur¹, selçuk dagdelen¹, tomris erbas¹

¹Hacettepe University, Endocrinology and Metabolism, Ankara, Turkey

Objective: Acromegaly is a disorder characterized by hypersecretion of GH and IGF-1. Excessive secretion of both hormones leads to soft tissue and bone overgrowth, alterations in physical appearance which in turn results in body image distortion, impairments in self esteem and changes in personality. In this study, our primary aim was to analyze whether alterations in body structure affect social media usage patterns in patients with acromegaly. Secondary aim was to evaluate the association between body image concerns and personality disorders.

Method: In this case-control study, 22 patients with acromegaly (A) and 22 subjects with prolactinoma or nonfunctional pituitary adenoma (C) were recruited. Information regarding social media usage habits, body image perception and personality characteristics were collected from following structured questionnaires; Turkish version of Body Image Concern Inventory (BICI), Rosenberg self esteem scale (RSES), personality belief questionnaire – short Turkish form (PBQ-SF), social media addiction scale-short form (SMAS-SF), acromegaly quality of life questionnaires (AcroQoL).

Results: Both groups were comparable in terms of age and gender distribution (F/M: A 12/10 vs C 15/7; age in years A: 44.7±2.5 vs C: 39.7±2.4). Patients with acromegaly were more concerned about their body image, (BICI score in A: 129.9 ±8.06 vs C 146.3±3.14, p= 0.001). The frequency of social media users (82% in A vs 86% in C p=0.42), and the social media addiction scores were similar in both groups (A 41.13±12 vs C 35.72±10.5, p=0.81). The most widely used social media platform in both groups was Instagram®. Patients with acromegaly were following celebrity accounts more frequently than control group (A 32% vs C 19%, p=0.02). Photo-editing behaviour was more frequent in acromegaly group (A 23% vs C 9%, p=0.013). Photo-editing behaviour in acromegaly patients was positively correlated with GH level at diagnosis (p<0.001). Photo-editing behaviour in patients with acromegaly was related with poor quality of life. Impaired body perception was related with avoidant, passive aggressive, obsessive compulsif and paranoid personality disorders. Also poor quality of life was associated with avoidant, paranoid, antisocial and passive aggressive personality disorders.

Conclusion: Patients with acromegaly have a poor body image, impaired self esteem and poor quality of life. Changes in physical appearance results in changes in personality, social media activities, social interactions. Psychosocial care should be a part of individualized treatment in patients with acromegaly.

Abstract-ID: 227

NEW THERAPEUTIC TARGETS IN SOMATOTROPINOMAS: SHP2 AND FGFR4

Facundo García Barberá¹, Liliana Sosa², Gilda Mezger², Florencia Picech², Juan De Batista³, Laura Cecenarro², Patricia Calafat³, Jorge Mukdsi², Juan Pablo Petiti²

¹Centro de Microscopia Electrónica, Facultad de Ciencias Médicas. Universidad Nacional de Córdoba, Córdoba, Argentina

²Centro de Microscopia Electrónica-Instituto de Investigaciones En Ciencias de la Salud-Facultad de Ciencias Médicas-Universidad Nacional de Córdoba, Córdoba, Argentina

³Hospital Privado de Córdoba, Córdoba, Argentina

Octreotide (OCT), a somatostatin analog, binds to SSTR2 to inhibit proliferation via SHP2 in somatotropinomas. In these tumors, FGFR4 receptor has been described as a prognostic and therapeutic biomarker. In addition, has been suggested that SHP2 is a key mediator in the signaling of SSTR2 and FGFR4, but its role in tumor growth and therapeutic response in GH-tumors is still unknown. Our aim was to assess whether SHP2 and FGFR4 modulate OCT effect. SHP2 and FGFR4 expression was evaluated in 54 human pituitary samples: GHx9, ACTHx9, NFx30, and 6 non-tumor tissue, as well as, in PDX NUDE mice pituitary tumor post-11-day OCT or SHP099 treatment (IHQ, WB). GH3 and patient-derived cells were treated with OCT, SHP2 (SHP099, 15 μ M) or FGFR4 (Blu99931, 100 nM) inhibitors. Viability (MTT) and proliferation (BrdU) were examined. pSTAT3-Tyr705 were analyzed by WB and IF. Python analyzed RNA-seq (GSE51618-GSE209903). Stats: Kruskal-Wallis, ANOVA, t-test, Chi2, Pearson. Bioinformatic analysis showed lower FGFR4 expression in GH-tumors compared to ACTH and NF tumors, while SHP2 levels were similar in all phenotypes. Gene expression data demonstrated a negative correlation between SHP2 and FGFR4, but positive with STAT3, particularly in GH-tumors. In our cohort, somatotropinomas exhibited elevated SHP2 expression compared to non-tumor tissue, unrelated to clinical factors. OCT-pre-treated patients displayed higher FGFR4 H-score than non-treated ones ($p < 0.01$). In vitro, SHP2 inhibitor decreased GH-secreting cells proliferation reducing pSTAT3 levels. Also, OCT induced translocation of SHP2 to the plasma membrane and pSTAT3 to the nucleus, whereas Blu99931 enhanced the anti-proliferative effect of OCT ($p < 0.001$). In PDX mice (GH-tumor), 11-day OCT treatment inhibited growth, lowered SHP2, and raised FGFR4 expression ($p < 0.001$) while SHP099 treatment induces a 22% of reduction in tumor volume. The results suggest the therapeutic potential of SHP2 and the use of FGFR4 inhibitors to enhance OCT treatment, particularly in patients with elevated FGFR4 expression or somatostatin analog resistance.

Abstract-ID: 257

**UNRAVELLING THE MOLECULAR MECHANISMS BEHIND X-LINKED ACROGIGANTISMS:
IDENTIFICATION AND VALIDATION OF ENHANCERS USING BIOCHEMICAL AND IN VIVO ASSAYS**

Alexia Grasso¹, Andrea Lania², maria caterina mione³, giampaolo trivellin⁴

¹*Irccs Humanitas Research Hospital, Laboratory of Cellular and Molecular Endocrinology, Milan, Italy*

²*1department of Biomedical Sciences, Humanitas University, Milan, Italy, 2irccs Humanitas Research Hospital, Milan, Italy., Department of Biomedical Sciences, Humanitas University, Irccs Humanitas Research Hospital, Milan, Italy., Department of Biomedical Sciences, Humanitas University, Irccs Humanitas Research Hospital, Milan, Italy., Enea Loc, Italy*

³*Experimental Cancer Biology, Department of Cellular, Computational and Integrative Biology, University of Trento, Trento, Italy*

⁴*Department of Biomedical Sciences, Humanitas University, Irccs Humanitas Research Hospital, Milan, Italy*

X-linked acrogigantism (X-LAG) is a condition that causes abnormally fast growth that begins early in life due to hypersecretion of growth hormone from pituitary neuroendocrine tumors (PitNETs). This pathology is associated with the duplication of *GPR101*, an orphan G protein-coupled receptor that becomes strongly upregulated in the PitNETs. Nowadays, clinical management of X-LAG patients is challenging and therapeutic control of abnormal growth requires a combination of multiple therapeutic and surgical approaches. Therefore, precisely characterizing the molecular mechanisms that boosts the expression of *GPR101* in PitNETs will contribute to develop specific treatments for X-LAG patients.

This study focuses on identifying enhancers - DNA sequences activating the expression of target genes - that by interacting with the *GPR101* promoter can drive the ectopic expression of the receptor in the pituitary gland. We are performing ChIP-sequencing assays for enhancer-associated histone marks (H3K4me1, H3K27me3, H3K27ac) in different subtypes of human PitNETs, including X-LAG patients. Moreover, we have generated zebrafish transgenic lines to conduct an *in vivo* characterization of candidate enhancers. One-cell-stage zebrafish embryos have been injected with a mix containing the *Tol2* transposase and a plasmid harbouring the enhancer of interest driving the expression of an eGFP reporter.

Six zebrafish lines, each with stable expression of a candidate enhancer that we have previously identified at the X-LAG locus, have been established. Screening of F1 animals revealed that three enhancers (eRBMX, eARHGEF6, and eVGLL1-intronic) are active, each showing a different and specific expression pattern of eGFP. Interestingly, the eVGLL1-intronic and eRBMX enhancers are active in the central nervous system of the zebrafish larva, mainly in regions located in the telencephalon and diencephalon (where the hypothalamus is located). Preliminary biochemical annotations of enhancer activity conducted in a tumor belonging to the Pit1 lineage supported the presence of regulatory sequences at the eVGLL1-intronic and eRBMX loci.

Overall, our study provides the first *in vivo* evidence towards the identification of the enhancer(s) that control the differential expression of *GPR101* in X-LAG. Moreover, we expect to identify additional pituitary-active enhancers genome-wide. Ultimately, these data will allow a deeper comprehension of the molecular mechanisms that control gene expression in the pituitary gland and have the potential to identify new therapeutic targets.

Friday, December 08th, 2023

EYRC Poster Presentations

Abstract-ID: 8

RADIOLOGICAL AND CYTOLOGICAL PREDICTORS OF LONG-TERM EFFECTIVENESS OF THE FIRST-GENERATION SOMATOSTATIN RECEPTOR LIGANDS (FG-SRLS) IN PATIENTS WITH ACROMEGALYEvgeny Pronin¹, Mikhail Antsiferov², Alexey Petraikin³, Vyacheslav Pronin², Tatiana Alekseeva¹, Anastasia Lapshina⁴, Liliya Urusova⁴, Anna Khoruzhaya³, Safi Tamaeva⁵¹Endocrinological Dispensary, Moscow Health Department, Moscow, Russian Federation²Endocrinological Dispensary, Moscow Health Department, Russian Medical Academy of Continuing Professional Education, Ministry of Health of Russian Federation, Moscow, Russian Federation³Scientific and Practical Clinical Center for Diagnostics and Telemedicine Technologies, Moscow Health Department, Moscow, Russian Federation⁴National Medical Research Center for Endocrinology, Ministry of Health of Russian Federation, Moscow, Russian Federation⁵I. M. Sechenov First Moscow State Medical University, Ministry of Health of Russian Federation (Sechenov University), Moscow, Russian Federation

Taking into account the syndromic status of acromegaly, it is relevant to search and stratify diverse predictors that reflect the sensitivity of somatotrophic tumors to drug therapy (DT).

The aim of this study was comparative assessment of the relative intensity of the tumor signal (RITS) on T2-weighted (T2-WI) MRI and receptor expression of densely and sparsely granulated somatotrophic tumors (DGST&SGST) in patients with acromegaly.

Materials and methods: 42 patients who underwent non-radical adenomectomy and received fg-SRLs (lanreotide 120 mg/28-56 days or octreotide 10-30 mg/28 days) were examined. According to immunohistochemical analysis, DGST was detected in 22 and SGST in 20 patients. The volume of the residual tumor was 1.8 ± 4.2 vs 1.8 ± 1.9 cm³ ($p=0.95$), the initial value of the IGF-1 index (IGF-1/ULN) was 2.8 ± 0.8 vs 2.6 ± 0.9 ($p=0.55$). Duration of DT was 27.1 ± 16.5 vs 32.8 ± 20.0 months. RITS was assessed quantitatively by comparing the area of interest with the gray matter of the brain on T2-WI. The obtained data on RITS were compared to the morphological diagnosis, receptor phenotype and final results of fg-SRLs treatment.

Results: It was found that DGST have low RITS on T2-WI compared to SGST: -16.6 ± 19.3 vs 17.2 ± 21.6 ($p < 0.0001$). During the ROC analysis, AUC was 0.893 (0.796-0.989). Predictors of sensitivity and specificity of RITS were 95% and 78%, respectively. The cut-off point for DGST was less than -6%. A direct correlation was revealed between RITS and the presence of «fibrous bodies» in tumor cells ($r=0.56$, $p=0.0001$), as well as an inverse correlation between RITS and the expression of the SSTR2 ($r=-0.68$, $p=0.000$), the difference and ratio between the SSTR2&SSTR5 [$r=-0.36$ ($p=0.022$) and $r=-0.30$ ($p=0.06$), respectively].

In patients with hypointense (DGST) and hyperintense (SGST) tumors, a difference in the expression of the SSTR2 was revealed: 10.4 ± 2.5 vs 6.2 ± 3.6 points according to IRS ($p=0.0006$), difference and ratio of the SSTR2&SSTR5: 7.6 ± 2.7 vs 0.6 ± 4.8 ($p=0.041$) and 3.6 ± 3.0 vs 1.5 ± 1.5 ($p=0.0074$), respectively. A negative correlation was revealed between the expression of the SSTR2, the difference/ratio between the SSTR2&SSTR5 and the final IGF-1 index during fg-SRLs treatment [$r=-0.34$ ($p=0.027$), $r=-0.57$ ($p=0.0001$), $r=-0.51$ ($p=0.0008$)]. During DT, final level of the IGF-1 index in patients with a hypointense signal was 1.0 ± 0.5 vs 1.5 ± 0.7 in the group of patients with a hyperintense signal on T2-WI ($p=0.012$).

Conclusions:

1. The method for determining RITS on T2-WI MRI allows to carry out differential diagnosis between DGST&SGST and predict the characteristics of receptor expression that determine the effectiveness of long-term use of fg-SRLs.
2. The prevalence of the SSTR2 in hypointense DGST plays a leading role in the implementation of the suppressive effect of fg-SRLs.

Abstract-ID: 19

SELLAR XANTHOGRANULOMA – A RARE AND CHALLENGING ENTITY

Valentim Lopes¹, Patrícia Brito², Sara Lopes², Ana Margarida Monteiro², Adriana De Sousa Lages³, Rui Ramos⁴, Rui Almeida⁴, Olinda Marques²

¹*Hospital de Braga, Endocrinologia, Braga, Portugal*

²*Serviço de Endocrinologia Do Hospital de Braga, Portugal*

³*Serviço de Endocrinologia Do Hospital de Braga, Faculdade de Medicina Da Universidade de Coimbra, Portugal*

⁴*Serviço de Neurocirurgia Do Hospital de Braga, Portugal*

Introduction:

Xanthogranuloma is a non-neoplastic histological entity characterized by a chronic granulomatous reaction to the presence of cholesterol crystals and may be secondary to haemorrhage, infarction, inflammation, and/or necrosis. Its occurrence in the sellar region is extremely rare, about 0.6 to 2.7% of all sellar masses, and its pathogenesis is still unclear.

Clinical case:

A 69-years-old male patient with a previous history of hypothyroidism (treated with 50 mcg of levothyroxine), type 2 diabetes mellitus, hypertension and obesity complained of asthenia, depressive humour and low sexual drive over the previous 2 months. Laboratory evaluation showed central hypogonadism (testosterone 20.6 ng/dL, FSH 2.3 mUI/mL, LH 1.1 mUI/mL and prolactin 20.1 ng/mL), without any hormonal hypersecretion associated, and a normocytic normochromic anaemia. Sellar MRI demonstrated a large right-sided heterogeneous 18 mm sellar lesion, with suspected intratumoral haemorrhage, Knosp 1, with suprasellar extension, slightly touching the optic chiasm. Neuro-ophthalmologic examination was normal. Treatment was started with testosterone enanthate 100 mg IM every 4 weeks and titrated up gradually to 200 mg IM each 3 weeks, with frank symptomatic improvement. 15 months later, the patient started complaining of gradual worsening of the visual acuity associated to left temporal hemianopsia during neuro-ophthalmologic re-evaluation. MRI was repeated and revealed a slightly increment of the lesion, mainly in its suprasellar component, with stability of its heterogeneous appearance. The patient was submitted to transphenoidal surgical treatment 3 months later, without immediate or delayed complications and with relevant improvement of visual symptoms. The histological evaluation revealed the presence of numerous foamy macrophages, hemosiderin deposits and cholesterol clefts, with absence of epithelial cell granulomas, compatible with a diagnosis of a pituitary xanthogranuloma. The immunohistochemistry revealed positivity for CD68 and vimentin in the macrophages and for synaptophysin in the normal adenohypophysis. 1 year after the surgery, the MRI demonstrates a residual cystic lesion and the patient remains under enanthate testosterone and levothyroxine supplementation without any additional hormone deficiency or other compressive symptoms with regular follow-up in endocrinology consultation.

Conclusion:

Sellar xanthogranuloma is a rare entity that usually manifests in young adult patients with hypopituitarism and mass effect symptoms. Its preoperative diagnosis is challenging as they do not have specific radiological features. Surgery is the standard treatment and, in the majority of the cases, the outcome is favourable, with low re-growth after surgery.

Abstract-ID: 20

RADIOTHERAPY FOR GROWTH HORMONE SECRETING PITUITARY ADENOMAS

Saodat Issaeva¹, Miles Levy², Zamira Khalimova³

¹Republican Specialized Scientific and Practical Medical Center of Endocrinology Uzbekistan, Tashkent, Uzbekistan

²University Hospitals of Leicester, United Kingdom

³Republican Specialized Scientific-Practical Medical Center of Endocrinology, Republican Center of Endocrinology, Republican Center of Endocrinology, Tashkent, Uzbekistan

Aim. Assess the change in the size of somatotropin in men and women before and after radiation therapy (RT) for acromegaly.

Materials and methods. The object of the study are 94 patients with somatotropic pituitary adenomas who received RT in a total dose of 45-60 Gy per 20-25 fraction every other day, only 2 patients received SRS CyberKnife 45 Gy.

The duration of the disease averaged 9.2±7.8 years. The follow-up period after RT averaged 7.36±8.1 years.

Results. We studied the effect of RT on the size of the formation and their change before and after RT, depending on gender. Since there are conflicting opinions in the literature on this issue, men and women also react differently to RT.

Analysis of the results shows that in men (in 84.6% of cases) and in women (in 84% of cases) macroadenomas were significantly more common ($p < 0.01$). The incidence of giant adenomas was significantly lower (11.5% and 13.2%, respectively), and microadenomas in our study were found in men in 3.4%, in women only in 2.9% (OR; 95% CI 3, 2 (0.211-1.97)). After RT, cases of microadenoma in men increased to 34.6% and in women to 33.8%. The frequency of macroadenomas decreased to 65.4% and 63.2%, respectively, due to shrinkage of giant and macroadenomas. The incidence of giant adenomas decreased to 2.9%.

It should be noted that only 2 women had a recurrence of somatotropinoma. This is explained by the fact that giant adenomas after RT decreased in size to macroadenomas, but one patient with a macroadenoma developed a relapse and the second patient had resistance to RT, which manifested itself with a high level of growth hormone and IGF-1 and continued growth of somatotropinoma.

Conclusion. Thus, radiation therapy is effective in GH-secreting pituitary adenomas, both in women and men, especially in the long-term period after RT.

Abstract-ID: 24

COMPLICATION OF ACROMEGALY AFTER RADIOTHERAPY

Saodat Issaeva¹, Zamira Khalimova²

¹Republican Specialized Scientific and Practical Medical Center of Endocrinology Uzbekistan, Tashkent, Uzbekistan

²Republican Specialized Scientific and Practical Medical Center of Endocrinology Uzbekistan, Tashkent, Uzbekistan, Uzbekistan

Aim. To study the dynamics of loss of pituitary functions and the incidence of complications in acromegaly on the background of radiotherapy (RT).

Materials and methods. The object of the study are 94 patients with somatotrophic hypertension who received RT. According to age indicators, the patients were divided into 3 groups: 1st age group - 22-44 years old - 53 patients (56.4%), 2nd group - 45-59 years old - 34 patients (36.2%), 3 group - 60-69 years old - 7 patients (7.4%).

Results: The analysis shows that the incidence of complications after RT in different age groups varies. The most common complication of acromegaly after RT was secondary hypothyroidism. Thus, in the I age group before RT, the frequency of secondary hypothyroidism was 33.3% and after RT their number increased to 55.6%, in the II group 13.6% and 63.6%; in group III before RT 23.5% and 76.5%; and in group IV 42.8% and 85.7%, respectively, also the highest rate of secondary hypothyroidism developed in old age.

Hypopituitarism is the most common late complication of radiotherapy. In group I, before RT it was not detected, after RT it was observed in 44.4% of patients. At the age of 30-44 years before RT, it was detected in 4.6% of patients and after RT there was an almost 12.8 one-time increase in this indicator, in the age group of 45-59 years, hypopituitarism before and after RT was detected in 5.9% and 58.8 % of patients, respectively, in group III cases of hypopituitarism were not detected, and after RT it was determined in 71.4% of patients.

SPTS was detected after RT in age groups I, II, III and IV - 11.1%, 13.6%, 17.7% and 14.3%, respectively.

Partial optic neuropathy (descending atrophy of the optic nerve) before RT in the I age group occurred in 44.4%, after RT their frequency increased to 55.6%. In group II, this figure was 45.5% and 54.5%; in the III age group 47.1% and 55.9%, in the IV age group in 42.9% and 71.4% of patients, respectively.

Conclusion. After RT, with lengthening of the post-radiation period, the volume of pituitary adenomas decreases, but the complication rates increase.

Abstract-ID: 30**VISUAL MORBIDITY IN MACROPROLACTINOMA: A RETROSPECTIVE COHORT STUDY**Yaron Rudman¹, Hadar Duskin-Bitan², Hiba Masri-Iraqi¹, Amit Akirov³, Ilan Shimon⁴¹Beilinson Hospital, Rabin Medical Center, Institute of Endocrinology, Petah Tikva, Israel²Endocrinology & Metabolism Institute, Rabin Medical Center, Beilinson Hospital, Petah-Tikva, Israel³Rabin Medical Center, Beilinson Campus, Petah-Tikva, Israel⁴Rabin Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Petah-Tiqva, IsraelObjective

To study the visual morbidity associated with macroprolactinoma and its outcomes following medical and surgical treatment, and to identify predictors of visual recovery.

Design

A single center retrospective cohort study.

Methods

We reviewed patient's data including clinical presentation, serial pituitary MRI, laboratory tests, visual symptoms and neuro-ophthalmologic examination, visual field tests, and optical coherence tomography tests. The main outcome was complete visual field recovery at the end of follow-up. Patient's baseline characteristics were investigated as predictors of visual recovery.

Results

The study cohort included 150 macroprolactinoma patients. Visual field defects at baseline were evident in 37 out of 121 men (30.6%) and 3 out of 29 women (10.3%, $p < 0.01$). Patients were followed for a median of 6.0 years (IQR, 2.9-10.6). Ten patients suffered from pituitary apoplexy (6 at presentation and 4 during follow-up), of whom 9 patients suffered from apoplexy-induced visual morbidity. Twenty-one patients had optic chiasm herniation into empty sella, of whom only 3 patients suffered from associated visual morbidity. At the end of follow-up, 24 out of 39 available visual field tests (61.5%) exhibited complete visual field recovery. Patients that achieved complete visual recovery had smaller macroadenomas [median (IQR), 30.5 mm (15.0-80.0) vs 42.0 mm (30.0-85.0), $p < 0.01$], lower serum prolactin levels [1414 ng/ml (489-3586) vs 4119 ng/ml (2715-6315), $p < 0.01$], lower rates of central hypogonadism (78.3% vs 93.3%, $p = 0.05$) and central hypothyroidism (20.8% vs 53.3%, $p = 0.04$), lower rates of compressive optic neuropathy (35.3% vs 87.5%, $p = 0.02$), and a better visual acuity (better than 6/8 in both eyes, 93.7% vs 28.6%, $p < 0.01$). In patients who required optic tract decompression at diagnosis ($n = 25$), we found no differences in visual recovery rates between surgically-treated (5 out of 11, 45.5%) and medically-treated (8 out of 14, 57.1%) patients ($p = 0.56$).

Conclusions

In our cohort of 150 macroprolactinoma patients, 26.7% of patients presented with visual field defects at baseline, with higher rates of visual field damage among men. Patients that achieved complete visual recovery had smaller macroadenomas, lower serum prolactin levels, lower rates of central hypogonadism and central hypothyroidism, lower rates of compressive optic neuropathy, and a better baseline visual acuity. Given the limited sample size, we found no differences in visual recovery rates between surgically-treated and medically-treated patients who required optic tract decompression.

Abstract-ID: 39

CARE TRAJECTORIES AND QUALITY OF LIFE OF SURGICALLY TREATED PATIENTS WITH A PROLACTINOMA: WHY DID THEY OPT FOR SURGERY?

Victoria van Trigt¹, Nienke Biermasz², Ingrid Zandbergen², Iris Pelsma², Leontine Bakker², Marco Versteegen³, Wouter van Furth³

¹*Leiden University Medical Center, Leiden, the Netherlands, Department of Medicine, Division of Endocrinology, and Center for Endocrine Tumors Leiden,, Leiden, Netherlands*

²*Department of Medicine, Division of Endocrinology, and Center for Endocrine Tumors Leiden, Leiden University Medical Center, Leiden, the Netherlands, Netherlands*

³*Department of Neurosurgery, Leiden University Medical Center, University Neurosurgical Center Holland, Leiden, The Netherlands., Netherlands*

Purpose: To describe care trajectories and quality of life in patients with prolactinoma, aiming to clarify the rationale for surgery.

Methods: Retrospective observational cohort study of consecutive patients with prolactinoma undergoing surgery from 2017 to 2019 at the referral center (RC), prior to surgery being considered a viable treatment option (i.e. PRolaCT study). Demographics and clinical data (type and duration of pretreatment and surgical indications, goals, and outcomes) were collected from patient records. Care trajectories were divided into three phases: (1)diagnosis and initial treatment, (2)endocrine treatment at the RC, and (3)surgical treatment. Quality of life after surgery was analyzed using the Leiden Bothers and Needs Questionnaire and SF-36.

Results: 40 patients were included (31 females (77.5%), median age 26.5 (14-63) years. Indications for surgery were dopamine agonist (DA) *intolerance* (n=31, 77.5%), *resistance* (n=6, 15.0%), and *patient/physician preference* (n=3, 7.5%). Patients were pretreated with DA (n=39 (97.5%)), and surgery (n=3 (7.5%)). Median disease duration at surgery was 4 (0-27) years. Primary surgical goal was total resection in 38 patients (95.0%), of which biochemical remission was achieved 6 months postoperatively in 23 patients (62.2%), and clinical remission in 6 patients (16.2%), missing data n=1. Data on quality of life will follow.

Conclusion: Care trajectories were highly individualized based on patient and tumor characteristics, as well as the multidisciplinary team's assessment (need for alternative treatment, surgical chances and risks). Most patients were pretreated pharmacologically and had broad variation in timing of referral, undergoing surgery as last-resort treatment predominantly due to DA intolerance. High quality imaging and multidisciplinary consultations with experienced neurosurgeons and endocrinologists enabling treatment tailored to patients' needs were prerequisites for adequate counseling in treatment of patients with prolactinoma.

Abstract-ID: 46**PHENOTYPICAL VARIATION OF A MUTATION IN LHX4 GENE WITHIN THE SAME FAMILY**

Catarina Cidade-Rodrigues¹, Graziella Pinto², Marie Legendre³, Michel Polak⁴

¹Centro Hospitalar Do Tamega e Sousa, Endocrinology Department, Penafiel, Portugal

²Hopital Universitaire Necker Enfants Malades, Assistance Publique Hopitaux de Paris, Pediatric Endocrinology, Gynecology and Diabetology Department, Paris, France

³Hopital Armand-Trousseau, Sorbonne Université, Assistance Publique Hopitaux de Paris, Molecular Genetics Department Laboratory, Paris, France

⁴Hopital Universitaire Necker Enfants Malades, Assistance Publique Hopitaux de Paris, Université Paris Cité, Pediatric Endocrinology, Gynecology and Diabetology Department, Paris, France

Introduction: *LHX4* gene is crucial for pituitary development/differentiation. These mutations are a rare cause of autosomal dominant congenital hypopituitarism. There is variability in manifestations, unclear phenotype-genotype correlation and incomplete penetrance. We present a case of a family carrying pathogenic *LHX4* mutation.

Clinical cases: **Twin 1:** Born at 37 weeks (2960kg, 48cm). Height at -1.5SD until 5 months, then delay to -4.5SD at 21 months; weight at -1 until 6 months, then stagnation at -3SD. Prominent forehead, retrognathism. At 21 months, diagnosed with growth hormone (GH) deficiency, treated with GH (4SD height gain). Developed central hypocortisolism at 7 years and central hypothyroidism at 9 years treated with hydrocortisone and levothyroxine. Language delay, dyslexia and attention deficit hyperactivity disorder (ADHD) at 20 months. Exome sequencing revealed a heterozygous nonsense variation c.351C>Ap.(Cys117*) in *LHX4* present also in the father, twin and older brother. **Twin 2:** Born small for gestational age [2.220kg, 45cm (1st percentile)]. At 21 months, height was at -1SD, weight at -2SD, IGF-1 26µg/L (46-150) but normal GH peak on glucagon stimulation test. Retrognathism. From 3.5 years, his growth declined to -1.5SD and weight to -2.5SD. GH deficiency at 4.5 years, treated with GH (height gain 3.5SD). Dyslexia, dysorthography and ADHD at 7 years. Both twins had +1SD height at 10 years. **Older brother:** Born at 40 weeks (3.900kg, 50cm). No growth delay, puberty at 12 years with dysorthography. **Father:** Asymptomatic, no psychomotor difficulties and normal height.

Discussion and conclusions: The observation of variable expressivity and incomplete penetrance of the same genotype within the same family (including identical-twins) suggests that other genetic and/or environmental factors with plasticity during pituitary development may influence the phenotype. Psychomotor developmental delay in *LHX4* mutations not explained by long-standing undiagnosed hypothyroidism has been reported once in literature. This is the first report of a *LHX4* pathogenic variation in identical-twins in whom psychomotor development accompanied/preceded hypopituitarism. We also report a patient with *LHX4* mutation and speech/learning difficulties, regardless of hormonal deficiency suggesting that *LHX4* plays a role in CNS development. In these patients, neurocognitive assessment is essential. Since there is risk of developing pituitary hormone deficiencies, clinical and hormonal surveillance are key.

Abstract-ID: 52

INTEGRATION OF PROTEOGENOMIC AND SINGLE-CELL SEQUENCING DATA ESTABLISHES A MOLECULAR CLASSIFICATION SYSTEM FOR PITNET: PREDICTING PROGNOSIS AND GUIDING DRUG THERAPY

Qilin Zhang¹, Boyuan Yao², Yao Zhao³

¹*Huashan Hospital, Department of Neurosurgery, Shanghai, China*

²*Huashan Hospital, Fudan University, Shanghai, China*

³*Huashan Hospital, Fudan University, Shanghai, China*

Objective:

The objective of this study is to integrate two molecular subtyping methods to establish a novel molecular classification system for PitNETs, which can predict the prognosis and guide drug therapy.

Methods:

In this study, we integrated and analyze the single-cell RNA sequencing data and multi-omics data into a new molecular subtyping system. We scored the molecular markers of each subtype identified by single-cell sequencing using the Gene Set Variation Analysis (GSVA) method and confirmed the feasibility of the integration in 800 additional samples.

Results:

By integrating the two subtyping methods, we identified that the EMT^{PRO} subtype of PitNETs mostly consisted of poorly differentiated PIT1 tumors, which showed high invasiveness, high recurrence rate, poor prognosis, and activation of EMT transcription factors ZEB2 and TWIST1. Immune infiltration was also observed in this subtype, suggesting potential for immunotherapy. Moreover, we found that most null cell adenomas and SF1 lineage tumors had similar molecular features, whereas silent corticotroph adenomas and corticotroph tumors were distinct with different clinical prognoses and drug targets.

Conclusions:

By integrating the data from our previous two sequencing studies, we established a molecular subtyping system for PitNETs, which can effectively predict the prognosis and guide drug therapy. This study provides new insights into the molecular heterogeneity of PitNETs and lays a foundation for precision medicine in the treatment of PitNETs.

Abstract-ID: 57

A PATHOGENIC PROTO-ONCOGENE RET MUTATION IN AN ACROMEGALY PATIENT

Sabrina Chiloiro¹, Ettore Domenico Capoluongo², Flavia Costanza³, Angelo Minucci⁴, Antonella Giampietro¹, Amato Infante⁵, Domenico Milardi¹, Claudio Ricciardi Tenore⁴, Maria De Bonis⁴, Simona Gaudino⁵, Guido Rindi⁶, Alessandro Olivi⁷, Laura De Marinis¹, Alfredo Pontecorvi¹, Francesco Doglietto⁷, Antonio Bianchi¹

¹*Division of Endocrinology and Metabolism, Fondazione Policlinico Universitario A. Gemelli Irccs - Rome, Italy, Department of Translational Medicine and Surgery, Università Cattolica del Sacro, Rome, Italy*

²*Department of Molecular Medicine and Medical Biotechnology, Federico II University, Naples, Italy, Department of Clinical Pathology and Genomics – Ospedale Per L'emergenza Cannizzaro – Catania, Italy*

³*Division of Endocrinology and Metabolism, Fondazione Policlinico Universitario A. Gemelli Irccs - Rome, Italy, Department of Translational Medicine and Surgery, Università Cattolica del Sacro, Rome, Italy, Italy*

⁴*Unit of Molecular Diagnostics and Genomics, Department of Laboratory Sciences and Infectious Diseases, Fondazione Policlinico Universitario A. Gemelli Irccs*

⁵*Department of Imaging, Radiation Therapy and Hematology, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Agostino Gemelli, Istituto DI Ricovero e Cura A Carattere Scientifico (Irccs), Rome, Italy*

⁶*Section of Anatomic Pathology, Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, Rome, Italy, Unit of Head and Neck, Thoracic and Endocrine Pathology, Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli Irccs; Roma European Neuro-Endocrine Tumor Society (Enets) Center of Excellence, Rome, Italy*

⁷*Department of Neurosurgery, Fondazione Policlinico Universitario A. Gemelli Irccs, Università Cattolica del Sacro Cuore, L.Go A. Gemelli, 8 - 00168, Rome, Italy*

Somatotropinomas are the pituitary tumor subtypes more genetically investigated for germline and somatic mutations. Although genetics clarified the origin of hereditary pituitary tumors in some cases of acromegaly, many gene alterations have not been identified yet.

A 48-year-old patient was affected by a cavernous sinus and bone-invasive somatotropinoma, resistant to first- and second-line medical therapies. The patient was also diagnosed with left breast cancer and right breast fibroadenoma. According to the somatotropinoma aggressive behavior and cancer history, a genetic study for germline mutations was performed through a specific panel designed for Pit-NETs. To our knowledge, we describe the first acromegaly patient with the RET gene pathogenic variant: c.2410G>A; p.Val804Met; rs79658334. The presence of RET fusions is well documented in breast cancers, but RET germline pathogenic variants have never been reported in breast cancer. After excluding all the other possible RET-associated pathologies, including multiple endocrine neoplasia (MEN)-2A and MEN-2B, we speculated that our patient was suggestive to be affected by Hereditary Cancer-Predisposing Syndrome (HCPS), since the association with this pathogenic variant is known in the literature. After the RET mutation finding, the patient's family underwent genetic screening, which resulted positive in the 25-year-old daughter for the same pathogenic variant. The pituitary hormonal assessment, until now, ruled out abnormalities, but the daughter was also diagnosed with right breast fibroadenoma. This finding supported the hypothesis that RET c.2410G>A pathogenic variant may cause HCPS. Given the genetic mutation, cancer history, and acromegaly, both our patient and her daughter followed close oncological surveillance.

In conclusion, our clinical case describes a new phenotype associated with RET mutation, represented by an acromegalic woman with breast carcinoma, suggesting that also pituitary tumors should be considered in the complex scenario of HCPS. Moreover, RET mutations may be included in the gene panel of somatotropinomas, in patients with aggressive tumors and suggestive clinical history, particularly in the context of clinical exome screenings.

Abstract-ID: 71

SINGLE-CELL TRANSCRIPTOMICS PINPOINTS PLACENTAL GROWTH FACTOR AND VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) RECEPTOR 1, BUT NOT VEGFA, AS PROMISING TARGETS IN GONADOTROPH TUMORS

Mirela Diana ILIE¹, Maxime Lepetit², Marie Chanal³, Alexandre Vasiljevic⁴, Emmanuel Jouanneau⁵, Olivier Gandrillon², Franck Picard², Gérald Raverot⁶, Philippe Bertolino³

¹Inserm U1052, Cnrs Umr5286, Cancer Research Center of Lyon, Lyon 1 University, Citi, Lyon, France

²École Normale Supérieure de Lyon, Lyon, France

³Inserm U1052, Cnrs Umr5286, Cancer Research Center of Lyon, Lyon 1 University, Lyon, France

⁴Inserm U1052, Cnrs Umr5286, Cancer Research Center of Lyon, Lyon 1 University, Pathology Department, Reference Center for Rare Pituitary Diseases Hypo, "groupement Hospitalier Est" Hospices Civils de Lyon, Lyon, France

⁵Inserm U1052, Cnrs Umr5286, Cancer Research Center of Lyon, Lyon 1 University, Neurosurgery Department, Reference Center for Rare Pituitary Diseases Hypo, "groupement Hospitalier Est" Hospices Civils de Lyon, Lyon, France

⁶Inserm U1052, Cnrs Umr5286, Cancer Research Center of Lyon, Lyon 1 University, Endocrinology Department, Reference Center for Rare Pituitary Diseases Hypo, "groupement Hospitalier Est" Hospices Civils de Lyon, Lyon, France

Context: Recent work has highlighted the importance of tumor microenvironment (TME) in the invasive and aggressive behaviour of gonadotroph tumors, suggesting promising therapeutic implications. TME-targeting therapies used so far in PitNETs include immune-checkpoint inhibitors and antiangiogenic treatments. Given that immune-checkpoint inhibitors are thought for several reasons to potentially be ineffective in gonadotroph tumors, in this work we focused on the potential of angiogenesis targeting. The antiangiogenic treatment used so far in PitNETs consists of bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF)-A, used as monotherapy in 18 cases, and sunitinib, a multi-tyrosine kinase inhibitor targeting VEGF receptors among other targets, used as monotherapy in three cases. Bevacizumab has stabilized tumor growth in around 60% of corticotroph and lactotroph tumors, while sunitinib has shown no effect so far. To date, no gonadotroph tumor was treated with TME-targeting therapies.

Aim: Explore VEGF family members and their cognate receptors to identify potential effective treatments for gonadotroph tumors.

Methods: Single-cell transcriptomics of seven freshly resected pituitary tumors (six gonadotroph and one silent corticotroph tumor).

Results: 24.471 cells coming from the six gonadotroph tumors and 3.052 cells coming from the silent corticotroph tumor passed the quality control. The ratio between tumor and TME cells was dependent on the analysed sample. Clustering analysis performed with Seurat confirmed the identification of tumor, stromal, endothelial, and immune cells in all tumors. In accordance with the rather good response to bevacizumab seen in corticotroph tumors, VEGFA was expressed by several cell types in the corticotroph tumor, notably by stromal cells, macrophages, and stem cells. Interestingly, in gonadotroph tumors, VEGFA was present in a very small amount, being expressed almost exclusively by a small subset of immune cells. VEGFB was the most expressed VEGF member in both the corticotroph and gonadotroph tumors, and was expressed by several cell types, notably tumor cells, normal anterior pituitary cells, stromal cells, macrophages, and stem cells. Interestingly, in gonadotroph tumors, the cluster with the most frequent expression of VEGFB was a small cluster of proliferating tumor cells. However, the pro- or anti-angiogenic role of VEGFB is still debated. In gonadotroph tumors, the next most expressed VEGF member was placental growth factor, which was specifically expressed by stromal cells. VEGFC and VEGFD were virtually absent. Regarding VEGF receptors, FLT1 (VEGFR1) was the most expressed by the endothelial cells from gonadotroph tumors, followed by KDR (VEGFR2). FLT4 (VEGFR3) was expressed in little amounts.

Conclusion: Our data suggest placental growth factor and its receptor, VEGFR1, would be better targets than VEGFA in gonadotroph tumors.

Abstract-ID: 72

PREDICTORS OF BIOCHEMICAL RESPONSE TO SOMATOSTATIN ANALOGS IN ACROMEGALY AFTER SURGERY - A REAL-LIFE PERSPECTIVE

Inês Meira¹, Helena Urbano Ferreira², João Menino³, Juliana Gonçalves⁴, Diana Alexandra Festas Silva⁵, Jorge Pedro⁶, Sandra Belo⁷, Davide Carvalho⁸, joana queiros⁹

¹*Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar Universitário São João, Serviço de Endocrinologia, Diabetes e Metabolismo, Porto, Centro Hospitalar Universitário São João, Serviço de Endocrinologias, Porto, Portugal, Lisboa, Portugal*

²*Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo, Medicine Faculty of University of Porto, Centro Hospitalar Universitário São João, Serviço de Endocrinologia Diabetes e Metabolismo, Lisboa, Portugal*

³*Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar Universitário São João, Porto, Portugal, Faculty of Medicine e Instituto de Investigação e Inovação Em Saúde, University of Porto, Porto, Portugal, Portugal*

⁴*Associação Dos Amigos Do Serviço de Endocrinologia Do Hospital de S. João, Faculty of Medicine of University of Porto, Department of Endocrinology, Matosinhos, Portugal*

⁵*Coimbra Hospital and University Centre, Endocrinology Department, Coimbra, Portugal*

⁶*Centro Hospitalar Universitario Sao, Medicine Faculty of University of Porto, Endocrinology, Porto, Portugal*

⁷*Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar São João, E.P.E., Faculdade de Medicina Da Universidade Do Porto, I3s – Instituto de Investigação e Inovação Em Saúde, Universidade Do Porto, Porto, Portugal*

⁸*Chus João, Faculty of Medicine, I3s University of Porto, Porto, Portugal*

⁹*Chusj, Portugal*

Introduction: First-generation somatostatin receptor ligands (fg-SRLs) are currently the first-line medical therapy for persistent or recurrent acromegaly following neurosurgical intervention. Different pretreatment biomarkers might influence the biochemical response to fg-SRLs.

Objective: This study aimed to investigate clinical, biochemical and radiological predictors of biochemical response to fg-SRL therapy in acromegaly patients previously submitted to neurosurgery.

Methods: Retrospective study of a cohort of acromegalic patients who underwent surgery between 2005 and 2023. IGF-1 levels were assessed prior to initiating medical treatment with fg-SRLs, and again at 6 to 12-month after initiating fg-SRLs therapy. Biochemical response was defined as insulin-like growth factor 1 (IGF-1) $\leq 1.3 \times \text{ULN}$ (upper limit of normal). Absolute IGF-1 reduction was also assessed. Univariate logistic and linear regression analyses were performed.

Results: The study included 53 patients (64.2% males, median age 46 years). Univariate analysis revealed that lower IGF-1 concentration before treatment (OR=0.089, $p=0.002$) and lower baseline fasting blood glucose levels (OR=0.985, $p=0.022$) were associated with a higher likelihood of achieving biochemical response. A positive association was observed between pretreatment IGF-1 concentration, growth hormone levels after oral glucose tolerance test, fasting plasma glucose at diagnosis, and absolute IGF-1 reduction ($\beta=0.531$, $p<0.001$; $\beta=0.341$, $p=0.042$; $\beta=0.522$, $p<0.001$, respectively). Patients with cavernous sinus invasion on imaging were less likely to achieve biochemical response (OR=0.075, $p=0.007$). Other radiologic tumor characteristics, namely tumor size and T2-weighted signal, were not predictors of biochemical response. T2 hyperintense signal was negatively associated with absolute IGF-1 reduction ($\beta=-0.468$, $p=0.050$).

Conclusion: Lower pretreatment IGF-1 concentration and lower fasting plasma plasmatic glucose levels were predictive of a biochemical response to fg-SRLs. Patients with higher baseline IGF-1 and higher fasting blood plasmatic glucose experienced a greater absolute decline in IGF-1, even though they did not reach the threshold for establishing biochemical control. These results must be considered when treating these patients, and other therapies must be considered if a complete biochemical response has not been obtained.

Abstract-ID: 74

PITUITARY INCIDENTALOMAS: EXPERIENCE OF AN ONCOLOGY CENTER

Sara Gil dos Santos¹, Raquel Calheiros¹, Pedro Souteiro¹, Joana Oliveira¹, Isabel Inácio¹, Ana Paula Santos¹, Isabel Torres¹

¹Portuguese Institute of Oncology of Porto, Endocrinology, Porto, Portugal

Introduction: Pituitary incidentalomas, lesions found on imaging studies performed for unrelated reasons, are being increasingly detected. Our aim was to describe pituitary incidentalomas found in an oncology center.

Methods: We searched for the terms “sela(r)”, “pituitary” and “hypophysis” in the reports of all CTs and MRIs performed between the 30th of September 2008 and the 8th of September 2021 and collected the patients’ data regarding demographics, clinical presentation and follow-up.

Results: We found 46 patients with incidentalomas, 3 of which were of pediatric age. Adults had a mean age of 57.8±14.7 years and most were women (26; 60.5%). The most common reason for imaging exam request was headache (11; 25.6%) and reevaluation of a previously know SNC lesion or non-pituitary lesion detected in another exam (11; 25.6%). Most pituitary lesions were found by MRI (67.4%) and the most frequently detected lesions were pituitary adenomas (24; 55.8%), followed by metastasis (8; 18.6%). Hypopituitarism was detected in 8 patients, most of which had metastatic disease (5; 55.6%). There was no evidence of hormonal hypersecretion, although 9 patients had no record of pituitary function evaluation. One patient underwent surgical treatment (2.3%), one patient was treated with radiotherapy (2.3%) and 2 patients showed initial improvement with chemotherapy (4.7%). Patients with metastases had a higher prevalence of death 3 months after incidentaloma diagnosis (p=0.015).

Conclusions: In an oncology setting, pituitary adenomas remain the most frequently detected incidentaloma but metastases assume a higher proportion of cases when compared to other series. Hypopituitarism was detected in a significant number of patients, emphasizing the need for an Endocrinology referral in these individuals.

Abstract-ID: 76

CCL2 EXPRESSION IN THE MICROENVIRONMENT OF PITUITARY NEUROENDOCRINE TUMORS: RELATIONSHIP WITH TUMORAGGRESSIVENESS, REFRACTORINESS AND EPITHELIAL-TO-MESENCHYMAL TRANSITION PATHWAY?

Fábio Reis¹, Micaella Miranda², Rita Joaquim², Catarina Miranda², Tiago Oliveira³, Maria Presa³, Claudia Faria⁴, Isidro Cortes-Ciriano⁵, Márta Korbonits⁶, Maria João Bugalho⁷, Ana Luísa Silva⁸, Pedro Marques⁹

¹Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (Chuln), Endocrinology Department, Ecogenética e Saúde Humana, Lisbon, Portugal

²Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (Chuln), Endocrinology Department, Lisbon, Portugal

³Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (Chuln), Pathology Department, Lisbon, Portugal

⁴Neurosurgery Department, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (Chuln), Lisbon, Portugal; Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina Da Universidade de Lisboa, Lisboa, Portugal, Lisbon, Portugal

⁵European Bioinformatics Institute, Wellcome Genome Campus, Hinxton, UK, European Molecular Biology Laboratory

⁶Barts and The London School of Medic, Queen Mary University of London, BA and the London School of Medicine, London, United Kingdom

⁷Hospital de Santa Maria, Faculdade Medicina de Lisboa, Endocrinology, Lisboa, Portugal

⁸Faculdade de Medicina Da Universidade de Lisboa, Faculty of Medicine, Lisbon University, Laboratório de Genética, Lisbon, Portugal

⁹Centre for Endocrinology, Pituitary Tumor Unit, Endocrinology Department, Hospital Cuf Descobertas, Lisbon, Portugal, William Harvey Research Institute, London, United Kingdom

Introduction: The crosstalk between tumor cells and microenvironment elements of pituitary neuroendocrine tumors (PitNETs), including cytokines, may modulate oncogenic mechanisms, tumor aggressiveness and response to treatment. CCL2 was previously identified as a key cytokine PitNET, but its biological role remains unknown. We aimed to study the role of CCL2 in defining the phenotype and outcomes of PitNETs, as well as in influencing the epithelial-to-mesenchymal transition (EMT) pathway and macrophage chemotaxis.

Methods: We included 86 PitNET patients who had surgery at our center between 2014-2020: 62 nonfunctioning-PitNETs (NF-PitNETs), 18 somatotroph tumors and 6 corticotroph tumors. CCL2 expression was studied by RT-qPCR and immunohistochemistry. CCL2 immunoreactivity was measured semi-quantitatively; macrophages were stained for CD68 and CD163; E-cadherin immunostaining was analyzed on the basis of its location relative to the cytoplasmic membrane, as percentage of complete, incomplete and absent E-cadherin membranous staining. *CDH1* (gene encoding E-cadherin) was also assessed by RT-qPCR. CCL2 expression was correlated with clinicopathological and outcome data, as well as with macrophage infiltrates and E-cadherin expression.

Results: In our cohort, 47.7% were males, age at diagnosis was 56±15yr (mean±SD), and mean follow-up was 6±4yr. *CCL2* mRNA expression did not differ among PitNET types, but corticotroph tumors had lower CCL2 immunoreactivities than NF-PitNETs (p=0.001) and somatotroph tumors (p=0.059). In the whole cohort, higher *CCL2* mRNA expression was seen in males, patients who had hypopituitarism at diagnosis, and in patients who more often required multimodal therapy, needed more treatments and had active disease at last-follow-up. Among somatotroph tumors, *CCL2* mRNA levels and serum IGF-1 at last follow-up correlated (r=0.517; p=0.040). Higher CCL2 immunoreactivity was associated with suprasellar extension, hypopituitarism at diagnosis and at last follow-up, and also correlated with tumor diameter (r=0.239; p=0.045). CD68+ and CD163+macrophages amount did not correlate with CCL2. *CCL2* mRNA expression levels negatively correlated with *CDH1* expression levels and with the percentage of tumor cells with complete membranous E-cadherin staining.

Conclusions: Our data suggest that CCL2 may have a relevant biological role in PitNETs leading to more aggressive, refractory and difficult-to-treat disease, and possibly activates EMT by downregulating E-cadherin. The lack of correlation between CCL2 and PitNET-infiltrating macrophages suggests that this single chemokine might not be critical in isolation for PitNET macrophage composition, and other chemokines may act synergistically in attracting macrophages to the PitNET microenvironment.

Abstract-ID: 77

CUSHING'S SYNDROME FROM AN ACTH PRODUCING NEUROENDOCRINE TUMOR PRESENTING AS CENTRAL HYPOTHYROIDISM AND HYPERGLYCEMIA

Nauman Jadoon¹

¹*NHS Greater Glasgow & Clyde, Endocrine, Glasgow, United Kingdom*

Introduction: Modulation of TSH secretion due to an elevated cortisol level has been documented, however it is rare for ectopic Cushing's syndrome to manifest as hypothyroidism. Here a case of ectopic Cushing's is reported who was referred with abnormal thyroid function test and was found to have Cushing's due to ACTH production from his neuroendocrine tumor.

Case Description: 37-year-old man who was diagnosed with neuroendocrine tumor 9 months back and was undergoing palliative chemotherapy presented to his general practitioner with 4 weeks history of increased lethargy and lower limb edema. He had his bloods taken and was found to have potassium of 2.9 mmol/L, TSH of 0.22 mU/L and Free T4 of 8.99 pmol/L respectively. The endocrine service was consulted to rule out adrenal insufficiency before starting thyroxine replacement given the symptoms. He was found to have a baseline cortisol level of 1583nmol/L with a 30 min post synacthen cortisol level of 1648nmol/L. His ACTH was checked which came back at 374ng/L. Rest of the pituitary profile showed low LH, FSH and IGF-1 but normal prolactin and unremarkable pituitary imaging. A diagnosis of severe Cushing's syndrome due to an ACTH-producing neuroendocrine tumor was made and he was started on Metyrapone. Hypothyroidism was likely due to severe hypercortisolism and was treated with thyroxine replacement. He was also found to be hyperglycemic, without any prior history of diabetes and was started on insulin for management of his blood glucose control. His symptoms improved with the above mentioned steps over the pursuing few weeks and his insulin requirements decreased. He was referred back to his oncology team for peptide receptor radionuclide therapy.

Discussion: Hypercortisolism can cause suppressed TSH and central hypothyroidism and there are various potential explanations for this effect. This case was unusual in that the presentation and referral to endocrine service was due to central hypothyroidism because of the challenges of diagnosing rapidly progressive Cushing's syndrome in a patient with metastatic neuroendocrine tumor.

Abstract-ID: 84

MEDICAL THERAPY IN ACTH-DEPENDENT CUSHING'S SYNDROME – EXPERIENCE FROM A PORTUGUESE TERTIARY HOSPITAL

Telma Moreno¹, Sara Varela Ribeiro², Juliana Gonçalves³, Pedro Rodrigues⁴, Jorge Pedro⁵, Sandra Belo⁶, Davide Carvalho⁷

¹Hospital de São João, Faculdade de Medicina Do Porto, Porto, Portugal

²Endocrinology Department, Chsj, 319, Portugal

³Associação Dos Amigos Do Serviço de Endocrinologia Do Hospital de S. João, Faculty of Medicine of University of Porto, Department of Endocrinology, Matosinhos, Portugal

⁴Endocrinology Department, Chvng/E, Faculty Medicine, Porto University, Vila Nova de Gaia, Portugal

⁵Centro Hospitalar Universitario Sao, Medicine Faculty of University of Porto, Endocrinology, Porto, Portugal

⁶Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar São João, E.P.E., Faculdade de Medicina Da Universidade Do Porto, I3s – Instituto de Investigação e Inovação Em Saúde, Universidade Do Porto, Porto, Portugal

⁷Chus João, Faculty of Medicine, I3s University of Porto, Porto, Portugal

Introduction: Endogenous Cushing's syndrome is a rare condition characterized by excessive glucocorticoid secretion with most cases being ACTH-dependent, mostly due to Cushing's disease (CD) or to ectopic ACTH secretion (ECS). Medical therapy can be used as first- or second-line treatment in severe hypercortisolism and in cases of persistent or recurrent cortisol excess. We aimed to describe our experience with patients undergoing treatment with ketoconazole and metyrapone at a Portuguese center.

Methods: Retrospective study of patients with ACTH-dependent Cushing's syndrome treated with ketoconazole and/or metyrapone from 2007 to July 2023 at a Portuguese tertiary hospital. Data was retrieved from electronic medical records. Hypercortisolism control was mostly assessed by 24-hour urinary-free cortisol (UFC) – patients were classified as strong or weak responders according to UFC decrease $\geq 50\%$ or $< 50\%$, respectively.

Results: Thirty-eight patients were medically treated during this period – 29 CD and 6 ECS patients were treated either with ketoconazole (K) or metyrapone (M) and 3 patients were on combination therapy. Regarding the monotherapy group, 24 patients (21 CD and 3 ECS) had previously undergone surgery and 6 CD were submitted to radiotherapy. In 10 patients (8 CD and 2 ECS) medical therapy was first-line treatment. Regarding the 29 CD patients, 16 (88.9%) under K and 9 (81.8%) patients under M showed UFC normalization at some point during follow-up. Fourteen (77.8%) patients on K and 8 (72.7%) on M were strong responders. Mean UFC decrease for K-treated patients was 365.25 $\mu\text{g}/\text{day}$ vs 150.19 $\mu\text{g}/\text{day}$ and for M-treated patients 883.92 $\mu\text{g}/\text{day}$ vs 136.41 $\mu\text{g}/\text{day}$ before treatment and at last visit, respectively. Twelve of the 18 patients on K discontinued it during follow-up, 2 (16.7%) of them due to hepatotoxicity; M was discontinued in 9 of 11 patients (in 2 (22.2%) cases due to mild side effects (nausea and alopecia)). We found no significant difference in CD patients regarding prior treatment(s) or baseline hypercortisolism parameters between strong vs weak responders. Regarding the 6 ECS, 1 (50.0%) patient treated with K and 3 (75.0%) patients on M were strong responders. The 3 patients on combination therapy showed initial UFC normalization but due to hypercortisolism progression 2 underwent additional treatments.

Conclusion: Our analysis shows a high rate of hypercortisolism control by medical therapy, especially for Cushing's disease, as 88.9% and 81.8% of patients on ketoconazole or metyrapone achieved UFC normalization at some point during follow-up, respectively. Importantly, few side effects occurred as only 2 (8.7%) out of 23 patients treated with ketoconazole presented with hepatotoxicity. Overall, medical therapy proved to be a safe effective treatment for hypercortisolism management.

Abstract-ID: 87

PITUITARY APOPLEXY: 23 YEARS OF EXPERIENCE AT A TERTIARY CENTER

Andreia Martins Fernandes¹, Teresa Pereira², Isabel Ribeiro³, Cláudia Amaral²

¹*Instituto Português de Oncologia de Coimbra Fg, Endocrinology, Coimbra, Portugal*

²*Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar Universitário de Santo António, Portugal*

³*Serviço de Neurocirurgia, Centro Hospitalar Universitário de Santo António, Portugal*

Introduction: Pituitary apoplexy (PA), a rare condition resulting from hemorrhage or infarction of the pituitary gland, is a potentially life-threatening endocrine emergency. Timely diagnosis is critical to reduce morbidity and mortality. Surgical intervention should be considered in the presence of deteriorating consciousness, severe visual impairment, or acute, persistent, or progressive visual field defects. Patients without or with mild neuro-ophthalmological manifestations can be managed conservatively under close monitoring.

Objectives: To assess clinical characteristics, management and outcomes of patients with PA at a tertiary center; and to compare outcomes between conservative and surgical approaches.

Material and methods: We performed a retrospective analysis of PA cases from January 2000 to August 2023.

Results: This study included 55 patients with PA (33 men) with a median age of 60 years (range:14-82). PA was the initial presentation in 59 (90.9%) patients. Five patients had a history of pituitary adenomas (2 non-functioning, 1 prolactinoma, 1 acromegaly, 1 ACTH-secreting). Predisposing factors were identified in 16 (29.1%) patients, with cranioencephalic trauma, major surgery, and hypertension being the most common risk factors. The predominant symptoms were headaches (89.1%), followed by nausea/vomiting (52.7%), ophthalmoplegia (32.7%), and decreased visual acuity (23.6%). At presentation, 68.9% (31/45) had hypogonadism, 69.6% (32/46) had adrenal insufficiency, 56.6% (30/53) had hypothyroidism, and 8.3% (2/24) had growth hormone deficiency. Most cases (96.3%) involved macroadenomas. MRI identified PA in 95.8% of cases, compared to CT scans, which did so in only 36.7%. Out of 55 patients, 32 (58.2%) underwent pituitary surgery, with 26 (81.3%) having surgery during the episode. Null-cell adenomas (25.8%) were the most prevalent based on immunostaining. In the latest follow-up (average duration of 83 months), 37 (67.3%) patients had hormonal deficiencies; 26 (70.3%) operated, 11 (29.7%) conservatively managed. Among operated patients, 17.2% (5/29) experienced resolution of hypopituitarism, while 38.9% (7/18) of non-operated patients with initial hypopituitarism achieved resolution. There was a recovery of ophthalmologic impairment in 62.5% (15/23) of operated patients and in 88.8% (8/9) of non-operated patients. Surgical patients had a significantly higher rate of hypopituitarism at the last consultation ($p=0.009$), whereas visual recovery was more prominent in the conservatively treated group ($p=0.025$).

Discussion: PA should be managed with a multidisciplinary approach. Although significant visual recovery occurs in both the surgical and conservative treatment groups, the pituitary function outcomes are less favorable. Our results suggest that patients with PA without neuro-ophthalmic signs or exhibiting mild and non-progressive signs can be safely managed conservatively.

Abstract-ID: 89

CLINICAL PRESENTATION, PREDICTIVE FACTORS AND MANAGEMENT OF PATIENTS WITH NELSON SYNDROME: A RETROSPECTIVE STUDY

Pierluigi Mazzeo¹, filippo ceccato¹, irene tizianel¹, giacomo voltan¹, martina lazzara¹, alessandro mondin¹, carla scaroni¹, mattia barbot¹

¹University Hospital of Padua, Endocrinology Unit, Padua, Italy

Background: Nelson syndrome (NS) is a severe condition that can occur in patients with Cushing's disease (CD) following bilateral adrenalectomy (BA).

Diagnostic criteria for NS are the radiological demonstration of pituitary tumour growth or the new detection of a pituitary lesion at MRI after BA.

To date, there are no predictive factors of NS. The aim of this study is to evaluate clinical, radiological and hormonal characteristics of patients with CD submitted to BA and to identify risk factors for NS development. The treatments for tumour re-growth and cardiometabolic complications were also recorded.

Patients and method: retrospective study on 27 patients followed at our Unit (M/F:8/19; median age at CD diagnosis 33 years, IQR 27-42) with at least 36 months of follow-up, submitted to BA surgery due to refractory CD. Clinical, radiological, basal and stimulated hormone data were evaluated at diagnosis and during follow-up (at 6, 24 months and last available visit).

Results: During follow-up (132 months, IQR 102-360), 8/27 patients (29%) developed NS after a median time of 34 months (IQR 26-54) from BA. Patients with NS tended to have a more precocious diagnosis of CD [29 (25-33 years) vs 35 (29-47 years), $p=0.082$] and higher ACTH levels after surgery two years after BA compared to those who did not develop NS [814 (502-2442) vs 81 (39-230) ng/L, $p=0.045$].

Interestingly, patients who did not develop NS took lower doses of fludrocortisone [0.05 (0.05-0.1) vs 0.1 (0.1-1.12) mg, $p=0.005$], but we noticed a tendency to take more hydrocortisone [30 (22.5-30mg) vs 22 (20-26mg), $p=0.08$].

Regarding comorbidities, 6/8 patients had also hypertension, but only 3/8 (37.5%) developed diabetes mellitus vs 53% of patients without NS ($p=0.22$).

There was no difference in NS incidence between patients who received radiotherapy before BA than dose untreated ($p=0.18$). Among NS, 6/8 patients required pituitary surgery and/or radiotherapy to manage tumour growth. Medical therapy was also tried in 6 cases, resulting in tumour progression (3 cases treated with cabergoline), disease stability (1 case treated with temozolomide and 1 with pasireotide LAR) and initial tumour shrinkage (1 case treated with temozolomide and pasireotide LAR).

Conclusions: In our cohort the prevalence of NS was closed to 30%. A higher increase in post-operatively ACTH seems to predict the future development of NS. Younger age at diagnosis might be a predisposing factor as well, whereas no hormonal and radiological features at diagnosis appear to be related to the development of this condition. Multimodal treatment is frequently required to control tumour growth with pituitary target drugs being only partially effective.

Abstract-ID: 99

THE VALUE OF DIGITAL QUANTIFICATION OF SOMATOSTATIN RECEPTOR SUBTYPES 2 AND 5 IMMUNOSTAINING IN GH-SECRETING PITUITARY TUMORS

Claudia Campana¹, Jessica Amarù², Angelo Milioto², Federica Nista³, Peter M van Koetsveld⁴, Anand Iyer⁴, Marica Arvigo², Diego Ferone², Leo J Hofland⁴, Federico Gatto⁵

¹Endocrinology Unit, Department of Internal Medicine, Division of Endocrinology, Erasmus Medical Center, Rotterdam, The Netherlands, Department of Internal Medicine and Medical Specialties, School of Medical and Pharmaceutical Sciences, University of Genova, Genova, Italy

²Endocrinology Unit, Department of Internal Medicine and Medical Specialties, School of Medical and Pharmaceutical Sciences, University of Genova, Genova, Italy

³Endocrinology Unit, Department of Department of Health Sciences (Dissal), School of Medical and Pharmaceutical Sciences, University of Genova, Genova, Italy

⁴Department of Internal Medicine, Division of Endocrinology, Erasmus Medical Center, Rotterdam, The Netherlands

⁵Endocrinology Unit, Irccs Ospedale Policlinico San Martino, Genova, Italy

Introduction: Somatostatin receptor subtype 2 (SST₂) immunohistochemistry (IHC) is a predictive factor for first-generation somatostatin receptor ligand (fg-SRLs) response in acromegaly patients. The semi-quantitative immunoreactivity score (IRS) has been proposed as the gold standard to evaluate SST₂ IHC expression. Recently, our group developed a quantitative method to determine SST₂ expression using an open-source digital image analysis (DIA).

Aims: To confirm the reliability of SST₂ evaluation using the DIA in a new cohort of GH-secreting pituitary tumors. To validate the DIA also for the evaluation of SST subtype 5 (SST₅). To correlate SSTs expression with fg-SRLs response, with both IRS and DIA methods.

Material and Methods: SST₂ and SST₅ expression in paraffin-embedded tissues of 42 GH-secreting pituitary tumors was assessed using both IRS and DIA. The DIA software calculates the staining intensity (intensity/area) and the percentage of positive cells (%PC-DIA) based on four representative images. The IRS was independently performed by two researchers. Correlations were performed evaluating the "total" SST₂ expression (IRS vs. intensity/area) and the SST₂ %PC (%PC-IRS vs. %PC-DIA). Response to fg-SRLs was evaluated as GH and IGF1 xULN %decrease from baseline to 6-month treatment (adjuvant therapy after surgery).

Results: Mean SST₂ IRS was 6.41±3.35, mean intensity/area was 0.1714±0.1354, and mean %PC-DIA was 63.42±29.67%. A good correlation was observed between DIA and IRS (rho=0.924 for "total" SST₂ expression, and rho=0.649 for %PC, both p<0.0001). As concerns SST₅, mean IRS was 4.66±3.26, mean intensity/area was 0.0722±0.0944, and mean %PC-DIA was 38.27±38.84%. Also for SST₅ quantification, a good correlation was observed between DIA and IRS (rho=0.872 and 0.748, respectively, p<0.0001).

Twenty-four out of 42 patients (57%) were treated with fg-SRLs after surgery. A significant positive correlation was observed between GH %decrease and SST₂ expression, quantified with DIA (intensity/area rho 0.707, %PC 0.625, p<0.005) and total IRS (rho 0.655, p=0.017), but not with the %PC-IRS (rho=0.356, p=0.123). A similar pattern was observed between IGF-1 xULN %decrease and SST₂ expression, with a significant positive correlation for both DIA parameters and total IRS (rho 0.517 to 0.617, p<0.05), but not for %PC-IRS (rho=0.235, p=0.334). No correlation was observed between GH or IGF-1 xULN %decrease and SST₅ expression.

Conclusions: The DIA is a reliable quantification method to assess both SST₂ and SST₅ expression. SST₂, but not SST₅, expression correlated with the GH and IGF-1 response to fg-SRLs. This correlation was statistically significant using both IRS and DIA only when "total" SST₂ expression was assessed. Conversely, the %PC correlated with treatment response only when evaluated using the DIA, thus showing the superiority of this quantitative method.

Abstract-ID: 100

IMPULSE CONTROL DISORDER AND CABERGOLINE TREATMENT: A SINGLE CENTER STUDY OF PATIENTS WITH HYPERPROLACTINEMIA

Martina Verrienti¹, Giulia Cristilli¹, Luigi Zerbinati², Beatrice Valier², Benedetta Gardini¹, Marta Bondanelli¹, Maria Chiara Zatelli³, Maria Rosaria Ambrosio¹

¹*Section of Endocrinology and Internal Medicine, University of Ferrara, Department of Medical Sciences, Ferrara, Italy*

²*Institute of Psychiatry, University of Ferrara, Department of Neuroscience and Rehabilitation, Ferrara, Italy*

³*University of Ferrara, Dept of Medical Sciences, Section of Endocrinology, Ferrara, Italy*

BACKGROUND. Dopamine agonists (DAs) are commonly used to treat hyperprolactinemia. Among DAs, cabergoline (CBG), a selective D2 receptor agonist, is currently recommended by clinical guidelines for its superior efficacy. The use of DAs has been linked to impulse control disorders (ICDs) in several neurological conditions where DAs are administered at higher doses, e.g., Parkinson's disease (prevalence: 2,6-34,8%). Recent studies have also suggested an association between ICDs and the use of CBG in the treatment of hyperprolactinemic patients (prevalence: 10-25%).

OBJECTIVE. To assess the prevalence of CBG-induced ICDs in patients with hyperprolactinemia. To evaluate the possible risk factors associated with ICDs development.

METHODS. We performed a single center observational study including 96 adults: N=54 cases (CBG-treated subjects for hyperprolactinemia), N=42 controls (healthy subjects or patients with non-secreting pituitary adenomas/empty sella). ICDs were investigated through a semi-structured psychiatric interview and ICDs-specific questionnaires (QUIP-S, PICS, HBI, GUS, CBS, EDI3).

RESULTS. According to PICS questionnaire, the prevalence of ICDs was 12.96% in the case group (M:F=2:1, $p>.05$) and 7.14% (M:F=4:1, $p>.05$) in the control group with no statistically significant differences. No behavioral factors (alcohol, smoking, BMI) nor endocrinological factors (PRL levels, tumor size or invasiveness according to Hardy-Wilson classification) appeared to be significant risk factors. Among the ICD cases, there was no significant difference in the median CBG dose (0.5 mg/week vs. 0.75 mg/week) or cumulative dose (288.2 mg vs. 295.25 mg) between patients with and without ICDs.

ICD cases exhibited a shorter duration of CBG-therapy than non-ICD cases: patients who had been on CBG for a shorter period were more likely to exhibit ICDs than those who had been on CBG for longer duration (4.81 ± 2.97 years vs. 10.02 ± 6.51 years, $p<.05$).

CONCLUSIONS. The prevalence of ICDs in patients undergoing CBG treatment for hyperprolactinemia in Italy appears to be low, with no statistically significant differences compared to the control group. Therapy duration may instead be a significant factor in the presentation of ICDs, which tend to manifest within the first 4-5 years of therapy. No correlations were identified between ICD onset and risk factors related to lifestyle or endocrinological variables. These findings, representing the first data collected from an Italian population, will need confirmation through a larger sample size.

Abstract-ID: 105

THE ROLE OF THE GH RECEPTOR POLYMORPHISM AS A PROGNOSTIC FACTOR OF VERTEBRAL FRACTURES IN ACROMEGALY PATIENTS RESISTANT TO FIRST-GENERATION SRLS AND TREATED WITH GH RECEPTOR ANTAGONIST (PEGVISOMANT) OR SECOND-GENERATION SRL (PASIREOTIDE LAR)

Flavia Costanza¹, Antonella Giampietro², Pier Paolo Mattogno³, Amato Infante⁴, Flavia Angelini⁴, Liverana Lauretti³, Alessandro Olivi³, Alfredo Pontecorvi², Francesco Doglietto³, Laura De Marinis², Antonio Bianchi², Sabrina Chiloire²

¹Division of Endocrinology and Metabolism, Fondazione Policlinico Universitario A. Gemelli Irccs - Rome, Italy, Department of Translational Medicine and Surgery, Università Cattolica del Sacro, Rome, Italy, Italy

²Catholic University of the Sacred Heart - Fondazione Policlinico Gemelli Irccs, Department of Endocrinology and Diabetology, Rome, Italy

³Catholic University of the Sacred Heart - Fondazione Policlinico Gemelli Irccs, Rome, Italy, Department of Neurosurgery

⁴Catholic University of the Sacred Heart - Fondazione Policlinico Gemelli Irccs, Rome, Italy, Department of Translational Medicine

Acromegaly is associated with skeletal fragility and increased prevalence of vertebral fractures (VFs). In recent years several authors tried to investigate predictor markers of bone fragility risk in this endocrine disorder. Two isoforms of GH receptor (GHR) have been described, which differ in the presence or absence of a transcript of exon 3 of the GHR gene. Both isoforms produce a functional receptor, but the exon 3-deleted isoforms (d3-GHR) have greater sensitivity to endogenous and recombinant GH than the full-length isoform (fl-GHR).

We conducted a longitudinal, retrospective, observational, single-center study to investigate the role of GHR polymorphism as prognostic factor of incidental VFs (I-VFs) in first-generation somatostatin receptor ligands (SRLs)-resistant acromegalic patients and treated with GHR antagonist (Pegvisomant) or second-generation somatostatin analogs (Pasireotide Lar).

72 patients with acromegaly were included in our study. 28 patients carried d3-GHR isoform, and 44 patients carried fl-GHR isoform. At baseline, all patients were affected by active acromegaly: 46 patients were treated with Pegvisomant, in combination with first-generation SRLs, and 26 were treated with Pasireotide Lar. At the last follow-up, 58 patients achieved biochemical control of acromegaly. 18 patients carried prevalent VF (P-VFs), while 14 patients experienced the occurrence of I-VFs. From the group treated with Pegvisomant in combination with first-generation SRLs, 32 patients carried fl-GHR polymorphism and 14 carried d3-GHR polymorphism. From the group treated with Pasireotide Lar, 12 patients carried fl-GHR isoform and 14 patients carried d3-GHR isoform. I-VFs occurred more frequently in patients carrying the fl-GHR isoform compared to d3-GHR ($p=0.04$); otherwise, I-VFs occurred more frequently in patients carrying the d3-GHR isoform than fl-GHR ($p=0.01$) and in patients with P-VFs as compared to patients without P-VFs ($p=0.05$).

All patients treated with Pegvisomant in combination with first-generation SRLs, carriers of fl-GHR isoform, and all patients treated with Pasireotide Lar, carriers of d3-GHR isoform, showed an increased risk of VFs. Thus the GHR polymorphism could assume greater relevance as a prognostic factor of VFs in acromegaly patients resistant to first-generation SRLs and treated with Pegvisomant or Pasireotide Lar. Additional studies on larger populations and with longer follow-up are needed to confirm our data and deepen the mechanisms underlying our findings. In the future, the knowledge of the GHR polymorphism may improve the therapeutic approach of acromegaly patients, tailored to the individual patient, in the context of personalized medicine.

Abstract-ID: 107

PROGNOSTIC INDICATORS IN PITUITARY ADENOMA SURGERY: A COMPREHENSIVE ANALYSIS OF SURGICAL OUTCOMES AND COMPLICATIONS.

George Riley¹, Nicolas Scheyer¹, Isabelle Merlot², Bruno Guerci¹, Marc Klein¹, Lea Demarquet¹

¹University Hospital of Nancy, Endocrinology, Diabetes and Nutrition, Nancy, France

²University Hospital of Nancy, Neurosurgery, Nancy, France

Objective: The primary aim of this study was to identify predictive factors associated with surgical success and the onset of de-novo clinically significant pituitary insufficiencies following endoscopic endonasal surgery (EES) for pituitary adenomas. Secondary and tertiary objectives explored the role of prolactin levels in predicting long-term hormonal insufficiencies.

Methods: A retrospective analysis was conducted on 211 patients who underwent EES. Logistic regression models were employed for the primary objectives, while Chi-square or Fisher's exact tests and Kruskal-Wallis tests were used for secondary and tertiary objectives. Patients were stratified into specific groups based on surgical indications and prolactin levels for nuanced analysis.

Results: Significant predictors for de-novo pituitary insufficiencies included male sex (OR 3.3, CI95% 1.3-8.1, p=0.01), immediate postoperative insufficiencies (OR 5.6, CI95% 2.8-11.1, p<0.001), and HYPRONOS criteria (OR 5.7, CI95% 1.6-20.9, p=0.008). For surgical success, preoperative insufficiencies (OR 0.7, CI95% 0.5-0.9, p=0.008), repeat surgeries (OR 0.1, CI95% 0-0.4, p=0.001), and gonadotroph or somatotroph adenomas were significant. Age and adenoma size were not predictive in multivariate analysis. No correlation was found between prolactin levels and postoperative or follow-up pituitary insufficiencies. A "dip-and-recover" prolactin pattern was observed postoperatively.

Conclusion: This study identifies key predictors for outcomes in pituitary surgery. For de-novo clinically significant pituitary insufficiencies, male sex, immediate postoperative insufficiencies, and HYPRONOS criteria were significant predictors. For surgical success, gonadotroph or somatotroph adenomas were positively associated, while preoperative insufficiencies and repeat surgeries were negative indicators. We observed no correlation between prolactin levels and pituitary insufficiencies. Our research is the first to employ individualized success criteria for EES, challenging existing perceptions about the role of age and adenoma size. These findings open avenues for nuanced, individualized preoperative risk assessment and postoperative management.

Abstract-ID: 118

DUAL-RELEASE HYDROCORTISONE IMPROVES BODY COMPOSITION AND THE GLUCOMETABOLIC PROFILE IN PATIENTS WITH SECONDARY ADRENAL INSUFFICIENCY – A PIECE OF EVIDENCE FOR INDIVIDUAL PRECISION TREATMENT

Nanna Thurmann Jørgensen¹, Victor Brun¹, Stina Borresen¹, Thea Christoffersen², Niklas Joergensen³, Torquil Watt¹, Ulla Feldt-Rasmussen⁴, Marianne Klose¹

¹Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, Department of Endocrinology and Metabolism, Copenhagen, Denmark

²Faculty of Health and Medical Sciences, Copenhagen University, Denmark, Department of Clinical Medicine, Copenhagen, Denmark

³Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, Department of Clinical Biochemistry, Glostrup, Denmark

⁴Department of Medical Endocrinology, Section 2132, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, Rigshospitalet, Endocrinology, Copenhagen, Denmark

Background and aim: Studies have suggested improved metabolic profiles in patients with adrenal insufficiency treated with dual-release hydrocortisone (Plenadren) compared with conventional hydrocortisone. This study investigates the effect of dual-release hydrocortisone compared with conventional hydrocortisone across a spectrum of essential health parameters: diurnal salivary cortisol/cortisone, body composition, markers related to bone health, glucose metabolism, and cardiovascular risk.

Material and methods: A prospective study of participants with secondary adrenal insufficiency and without diabetes mellitus (N = 27, 24 men) who were on stable treatment for all other pituitary deficiencies. The outcomes were measured at baseline during stable conventional hydrocortisone treatment and repeated 16 weeks after a switch in treatment to dual-release hydrocortisone.

Outcomes: Diurnal (0700, 1200, and 2300 hours) salivary cortisol and cortisone, body composition assessed by Dual-Energy X-ray absorptiometry scan, six bone status indices (serum type I N-terminal procollagen [PINP], collagen type I cross-linked C-telopeptide [CTX], osteocalcin, receptor activator kappa-B [RANK] ligand, osteoprotegerin, and sclerostin), lipids, haemoglobin A_{1c} (HbA_{1c}), and 24-hour blood pressure.

Results: The salivary cortisol area under the curve (AUC) was lower after treatment with dual-release hydrocortisone but did not reach significance (difference [sem]: -55.9 (1.3) nmol/L/day, $P = 0.06$). Salivary cortisone was lower at 2300 hours (-1.7 (0.5) nmol/L, $P = 0.02$), but the AUC did not change ($P = 0.9$). Also, mean total and abdominal fat mass (-1.4 (0.4) and -0.2 (0.09) kg, $P = 0.003$ and 0.02 , respectively), and HbA_{1c} decreased (-1.1 (0.4) mmol/mol, $P = 0.02$). Osteocalcin decreased (-7.0 (3.1) µg/L, $P = 0.03$) whereas sclerostin increased (41.2 (9.0) pg/mL, $P = 0.0001$). The remaining bone markers, lipids, and 24-hour blood pressure levels were unchanged.

Conclusion: This study suggests that a shift to dual-release hydrocortisone leads to lower cortisol exposure late evening, along with a more favourable metabolic profile and body composition. In contrast, however, decreased bone formation with increasing sclerostin might indicate a negative impact on bones. Together with previously published data on quality of life from this study group, our results support the need for individualised hydrocortisone substitution therapy in patients with secondary adrenal insufficiency.

Abstract-ID: 122

THE DIFFERENTIAL DIAGNOSIS BETWEEN CUSHING'S DISEASE AND PSEUDOCUSHING SYNDROME IN A PRE-AGONIC PATIENT.

Simone Antonio De Sanctis¹, sabrina chiloiro¹, eloisa sofia tanzarella², filippo bongiovanni³, antonella giampietro¹, gennaro de pascale⁴, laura de marinis⁵, massimo antonelli⁶, alfredo pontecorvi⁷, antonio bianchi¹

¹*Pituitary Unit, Fondazione Policlinico Universitario A. Gemelli Irccs, Università Cattolica del Sacro Cuore, Rome, Italy*

²*Dipartimento DI Scienze Biotecnologiche DI Base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, 00168 Roma, Italy, Dipartimento DI Scienze Dell'emergenze, Anestesiologiche e Della Rianimazione, Fondazione Policlinico Universitario A. Gemelli Irccs, 00168 Roma, Italy*

³*Department of Emergency, Intensive Care Medicine and Anesthesia, Fondazione Policlinico Universitario A. Gemelli Irccs, Rome, Italy, Department of Anesthesiology and Intensive Care Medicine, Catholic University of The Sacred Heart, Fondazione 'policlinico Universitario A. Gemelli' Irccs, L.Go F. Vito, 00168, Rome, Italy*

⁴*Dipartimento DI Scienza Dell'emergenza, Anestesiologiche e Della Rianimazione, Fondazione Policlinico Universitario A Gemelli Irccs, Rome, Italy*

⁵*Pituitary Unit, Fondazione Policlinico Universitario A. Gemelli Irccs, Università Cattolica del Sacro Cuore, Rome, Italy.*

⁶*Dipartimento DI Scienze Dell'emergenza, Anestesiologiche e Della Rianimazione, Policlinico Universitario A. Gemelli Irccs, Rome, Italy*

⁷*Department of Translational Medicine and Surgery, Unit of Endocrinology, Università Cattolica del Sacro Cuore-Fondazione Policlinico "Gemelli" Irccs, Largo Gemelli 8, I-00168 Rome, Italy*

Introduction: The pseudo-Cushing's encompass several disorders that can occur in high-stress situations, such as the sepsis, and that show biochemical features like those of Cushing's syndrome. We present a case with difficult differential diagnosis, for overlapping laboratory findings.

Case description: A 74-year-old man was admitted to our hospital for worsening dyspnoea since a month, 15 kilograms weight loss in the previous months, asthenia, hypotonia and muscle hypotrophy. In past medical history: glucose intolerance in treatment with metformin, depression in treatment with mirtazapine and vortioxetine and pancreatic intraductal papillary mucinous neoplasm (IPMN). Due to the onset of acute hypoxic-hypercapnic respiratory failure, the patient was treated with not-invasive ventilation and then admitted to the intensive care unit, for pneumonia and respiratory failure due to Meticillin-sensitive Staphylococcus aureus (MMSA) and Klebsiella Aerogenes. Antibiotic therapy was started according to the results of the antibiograms and sepsis. The neurological assessment showed a severe strength deficiency of the neck flexors and four limbs and hypophonia, reflexes were not revocable. No abnormalities in ocular motility, palpebral ptosis and muscular or lingual fasciculations were detected. Electromyography of deltoid muscles, brachial biceps and right rectus femur documented a method of recruitment of the myopathic type, suggestive for a sporadic late onset nemaline myopathy (SLONM). During the treatment in ICU, the patient underwent endotracheal intubation for the worsening of respiratory function and inotropic drug therapy was introduced for the development of septic shock. According to patient's clinical condition, hormones were tested showing an ACTH-dependent hypercortisolism. The results of Nugent, Liddle and the dexamethasone suppressed CRH stimulation tests suggested a not-neoplastic ACTH-dependent hypercortisolism. The pituitary contrasted magnetic resonance image showed a gland hypertrophy and the abdominal computed tomography (CT) ruled out adrenal lesions. Unfortunately, the patient developed a multi-organ failure, and at least died. The autopsy finding confirmed the absence of pituitary and other neuroendocrine tumours and showed a bilateral adrenal hypotrophy.

Conclusions: Our clinical case described a patient with pseudo-Cushing's syndrome during sepsis and pre-agonist phase, with difficult differential diagnosis, in which the combination of the low-dose dexamethasone suppression test and the CRH test allowed a conclusive and correct diagnostic orientation.

Abstract-ID: 123

A PITUITARY METASTASIS FROM OCCULT NEUROENDOCRINE TUMOR

Luigi Demarchis¹, Sabrina Chiloiro¹, Maria Grazia Maratta², Liverana Lauretti³, Antonella Giampietro¹, Giovanni Schinzari⁴, Rosalinda Calandrelli⁵, Simona Gaudino⁵, Laura De Marinis⁶, Guido Rindi⁷, Alfredo Pontecorvi⁶, Alessandro Olivi⁸, Giampaolo Tortora⁴, Francesco Doglietto⁸, Antonio Bianchi⁶, Pier Paolo Mattogno⁸, Marco Gessi⁹

¹Pituitary Unit, Fondazione Policlinico Universitario A. Gemelli Irccs, Università Cattolica del Sacro Cuore, Rome, Italy.

²Medical Oncology, Fondazione Policlinico Universitario Agostino Gemelli Irccs, Rome, Italy.

³Neurosurgery Unit, Department of Neurosciences, Fondazione Policlinico Universitario Agostino Gemelli, Istituto DI Ricovero e Cura A Carattere Scientifico (Irccs), Rome, Italy.

⁴Medical Oncology, Fondazione Policlinico Universitario Agostino Gemelli Irccs, Rome, Italy

⁵Uoc Radiologia e Neuroradiologia, Dipartimento DI Diagnostica Per Immagini, Radioterapia Oncologica Ed Ematologia, Rome, Italy

⁶Pituitary Unit, Fondazione Policlinico Universitario A. Gemelli Irccs, Università Cattolica del Sacro Cuore, Rome, Italy

⁷Anatomic Pathology Section, Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, Roma, Italy

⁸Neurosurgery Unit, Department of Neurosciences, Fondazione Policlinico Universitario Agostino Gemelli, Istituto DI Ricovero e Cura A Carattere Scientifico (Irccs), Rome, Italy

⁹Division of Pathology, Fondazione Policlinico Universitario A. Gemelli Irccs, Rome, Italy

Background: Pituitary metastases are rare and account around 1% of surgically treated pituitary lesions. Despite the low incidence, pituitary metastases may present with major symptoms such as headache, visual disturbances and visual field, for the compression effect on surrounding structures. Ultimately, damage to the pituitary may be associated with hypopituitarism and electrolyte disturbances.

Clinical case: A 57-year-old male patient was admitted to our hospital for ptosis, lacrimation and diplopia, previously treated with corticosteroids without benefit. A brain contrasted MRI examination showed a sellar lesion, in contact with the optic chiasma, infiltrating the right cavernous sinus, the clivus and the clinoid. Biochemical and hormone examinations showed slight hyperprolactinemia (47 ng/mL) in absence of electrolyte disturbances and deficits of pituitary hormones. The visual field examination detected a left superior-temporal campimetric deficit. Pre-surgery chest X-ray was negative. A sub-total transsphenoidal excision of the lesion was conducted and histologic examination identified a *"neoplasm with well-differentiated neuroendocrine morphology, relatively monomorphic round cells, intense expression of synaptophysin, chromogranin, 2A-somatostatin receptor, insulinoma-associated protein-1 (INSM1), thyroid transcription factor-1 (TTF1). Neoplastic cells were Pit1-, Tpit-, GATA3-, SF1-, CDX2-, ISLET1-, CAM5.2- and AE1/AE- negative. Proliferative index (MIB1) was 5-7%. Comment: localization of a neuroendocrine tumor (NET). Immunohistochemical pattern suggests a pulmonary origin (possible atypical carcinoid, NET G2)".* The patient underwent a 68-Gallium-DOTA-TOC Positron Emission Tomography/computed tomography (PET-CT) showed the residual sellar tumor with increased SSTR expression. A contrasted total body CT confirmed the residual neoplasia of maximum diameter of 24 millimeters in the right lateral and posterior sellar region, eroding the lamina quadrilateralis and the ipsilateral posterior clinoid process, extending extra compartmentally into the cavernous sinus, encompassing the intracranial portion at the internal carotid artery. Finally, the patient underwent 18-F-fluorodeoxyglucos PET-CT, which detected a more functionally active area in the right parasellar region. All radiological investigations did not reveal the primary tumour and other metastasis. Therefore, according to NET grading, non-detection of primary tumor and persistence of local disease, it is decided to treat the patient with somatostatin receptor ligand and to re-evaluate the status of disease, also considering the possibility of radiotherapy on the residual tumor.

Conclusions: our case is intended to emphasize the importance of considering the pituitary not only as a site of primary tumor but also as a possible site of metastasis, mainly from breast, lung, and colon cancers, without excluding firstly possible rarer primaries as occult or other side of NETs.

Abstract-ID: 124

PROGRAMMED CELL DEATH LIGAND-1 (PD-L1) EXPRESSION IN NON-FUNCTIONING PITUITARY NEUROENDOCRINE TUMOURS

Mariana Lopes-Pinto¹, Rita Joaquim², Tiago Oliveira³, Dolores López-Presa³, Cláudia C.Faria⁴, Márta Korbonits⁵, Maria João Bugalho⁶, Ana Luísa Silva⁷, Pedro Marques⁸

¹Endocrinology Department, Centro Hospitalar Universitário Lisboa Norte, Lisbon Portugal, Endocrinology

²Endocrinology Department, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (Chuln), Lisbon, Portugal

³Pathology Department, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (Chuln), Lisbon, Portugal

⁴Neurosurgery Department, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (Chuln), Lisbon, Portugal, Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina Da Universidade de Lisboa, Lisbon, Portugal

⁵Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, UK

⁶Endocrinology Department, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (Chuln), Lisbon, Portugal, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

⁷Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal, Instituto de Saúde Ambiental Da Faculdade de Medicina Da Universidade de Lisboa, Lisbon, Portugal

⁸Pituitary Tumour Unit, Endocrinology Department, Hospital Cuf Descobertas, Lisbon, Portugal, Faculdade de Medicina, Universidade Católica Portuguesa, Lisbon, Portugal

INTRODUCTION: Increased expression of programmed cell death-1 (PD-1) and PD ligand-1 (PD-L1) has been associated with poorer outcomes in different cancers. PD-L1 expression has been shown in Pituitary Neuroendocrine Tumours (PitNETs); however, its biological role and prognostic usefulness remains unclear. We aimed to assess the usefulness of PD-L1 expression as a marker of aggressive disease and clinical outcomes in patients with non-functioning PitNETs (NF-PitNETs).

METHODS: PD-L1 expression was studied by RT-qPCR using RNA extracted from 64 fresh-frozen tumour tissues from patients with NF-PitNETs who underwent surgery at our centre between 2014-2020. Fold difference in mRNA expression was calculated using $\Delta\Delta Ct$ method: PD-L1 levels were normalized to the expression levels of endogenous control gene TBP per sample, and normalized values were then expressed relative to those of a reference sample consisting of normal human tissues. Two subgroups were defined: NF-PitNETs with high PD-L1 expression (HighPD-L1) for cases with 2-fold increased PD-L1 expression (n=10), and low PD-L1 expression (LowPD-L1) when PD-L1 expression was below 2-fold (n=54). Different clinico-pathological features and outcome parameters were compared between these two subgroups.

RESULTS: In our cohort 53.1% were males, and the age at NF-PitNET diagnosis was 59.5 ± 12.3 yr (mean \pm SD). The mean follow-up duration was 71.9 ± 44.9 months. LowPD-L1 tumours showed a tendency to be associated with hyperprolactinemia and secondary hypothyroidism at diagnosis (p=0.79 and p=0.81 respectively). There were no significant differences between the HighPD-L1 and LowPD-L1 subgroups in terms of the various clinico-pathological features we analysed, including cavernous sinus invasion and Ki-67, neither regarding outcome parameters suggestive of refractory or difficult-to-treat PitNET disease, including rates of radiotherapy, multimodal or multiple treatment approaches, active disease at last follow-up, and total number of pituitary surgeries.

Conclusions: The expression of PD-L1, at least at the mRNA level, may not be biologically relevant in determining tumour invasiveness, aggressiveness or refractoriness to treatment in patients with NF-PitNETs, neither seem to have any potential role as a prognostic biomarker in NF-PitNETs.

Abstract-ID: 125

THE ACRO-TIME SCORE: A CLINICAL, PATHOLOGY AND IMMUNE MODEL PREDICTING RESPONSE TO CONVENTIONAL SRLS IN ACROMEGALY

Sabrina Chiloiro¹, Antonella Giampietro², Flavia Angelini³, Marco Gessi⁴, Liverana Lauretti⁵, Pier Paolo Mattogno⁵, Rosalinda Calandrelli⁶, Angela Carlino⁴, Simona Gaudino⁶, Alessandro Olivi⁵, Alfredo Pontecorvi², Francesco Doglietto⁵, Antonio Bianchi²

¹Department of Endocrinology, Catholic University of the Sacred Heart, Rome, Italy

²Department of Endocrinology, Gemelli University Hospital, Rome, Italy

³Department of Endocrinology, Gemelli Hospital, Rome, Italy, Italy

⁴Department of Human Pathology, Gemelli University Hospital, Rome, Italy

⁵Department of Neurosurgery, Gemelli University Hospital, Rome, Italy

⁶Department of Imaging, Gemelli University Hospital, Rome, Italy

Introduction: Somatotropinomas are benign pituitary tumors, with a heterogenous biological and clinical behavior. The control of acromegaly is reached in 25%-65% of first generation somatostatin ligands (fg-SRLs) treated patients. The tumor microenvironment reflects the interaction between tumor cells and the host immune system and may potentially regulate tumor behavior and therapy outcome. We aim to develop a scoring system that includes clinical, pathological and immune markers to early identify fg-SRLs resistant acromegaly patients.

Patients and methods: 43 consecutive acromegaly patients were included according the following criteria (1) first line treatment with surgery, (2) post-surgical fg-SRLs therapy (3) availability of tumor specimens for experimental analysis. patients not-naïve to acromegaly therapies before surgery, with history of radiotherapy of head and neck within 10 years before pituitary surgery, with immune-related disease were ruled out.

Results: Eighteen patients (41.9%) were fg-SRLs resistant: 14 were females (77.8%), with median age of 36.5 (IQR:13) and cavernous sinus invasion in 12 cases (66.7%). At histological examination, Ki-67 was <1.5% in 17 cases (39.5%). SSTR2A Volante scores were 0-1 in 5 cases (11.6%) and 2-3 in 38 cases (88.4%). Tumor-infiltrating CD4+ lymphocytes was 4.9/HFP (IQR: 8), CD8+ lymphocytes was 11/HFP (IQR:14) and CD68+ cells was 60/HFP (IQR:69). The ratio CD68+/CD8+ cells was 5.2 (IQR: 5). We analysed 18 clinical, pathological and immune features as possible predictors of fg-SRLs response. Fg-SRLs resistance was associated to age at acromegaly diagnosis <37 years (AUC: 0.72 OR: 2 95%IC: 1.1-4 p=0.04), cavernous sinus invasion (OR: 9.3 95%IC:1.4-61 p<0.001), Ki-67>1.5% (OR: 3.2 95%IC:1.2-13.1 p=0.04), score 0-1 of SSTR2A (OR: 2.7 95%IC: 1.7-4.1 p=0.03), ratio CD68+/CD8+ cells<5.7/HPF (AUC: 0.709 OR: 4.9 95%IC:1.2-19.2 p=0.03) and persistence of post-surgery residual tumor (OR: 2.5 95%IC:1.3-4.7 p=0.004). These variables were analysed in a logistic regression model, yielding a beta coefficient of 3.7 for age >37 years; of -3 for cavernous sinus invasion; of -0.2 for Ki-67>1.5%; of 20 for SSTR2A score 2-3; of -0.9 for CD68+/CD8+cells ratio >5.7/HFP; and of -0.9 for persistence of post-surgery residual. We assigned a score to each covariate proportional to its beta coefficient, yielding a cumulative score for each patient. The score values ranged from 18.5 to 24 in cases responsive to fg-SRLs and from -5.5 to 21.5 in fg-SRLs resistant cases. A score <19 was chosen as cut-point to identify fg-SRLs resistance (AUC: 0.059 p<0.001 95%IC: 0.0-0.126). A score <19 was associated to fg-SRLs resistance in 84.6% of cases (p<0.001 OR: 3.7 95%IC:1.7-6.7).

CONCLUSIONS: This new score integrates clinical, pathological, immunological data and may predict resistance to fg-SRLs and the need of second line treatments.

Abstract-ID: 128

HEPATIC STEATOSIS INDEX AS A NON-INVASIVE MARKER FOR LIVER STEATOSIS IN PATIENTS WITH ENDOGENOUS CUSHING SYNDROME, ERCUSYN KRAKOW DATABASE

Mari Minasyan¹, Aleksandra Gamrat², Alicja Hubalewska-Dydejczyk³, Elena Valassi⁴, Aleksandra Gilis-Januszewska³

¹*Endocrinology, Oncological Endocrinology, and Nuclear Medicine Department, University Hospital, Krakow, Poland, Endocrinology Department, Cracow, Poland*

²*Chair and Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland*

³*Endocrinology, Oncological Endocrinology, and Nuclear Medicine Department, University Hospital, Krakow, Poland, Chair and Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland*

⁴*Endocrinology and Nutrition Department, Germans Trias I Pujol Hospital and Research Institute, Badalona, Spain,*

Introduction: Liver Steatosis(LS) can be one of the metabolic complications of Cushing Syndrome(CS). The data on the impact of cortisol on liver function are very limited, the single study reported the 20% prevalence of LS in CS. However, the frequency seems to be much higher. Hepatic Steatosis Index (HSI) predicts LS based on ALT, AST, BMI, sex and co-existence of diabetes mellitus/impaired glucose intolerance. It can identify candidates for further liver examinations.

Objectives: To evaluate the prevalence of LS in patients with CS at the time of diagnosis by using HSI. **Methods:** We analyzed retrospectively adult patients from the ERCUSYN, Krakow database with complete HSI data available. The HSI score was calculated using the following formula: $8 \times (\text{ALT}/\text{AST}) + \text{BMI} + 2(\text{if type 2 diabetes}) + 2(\text{if female})$. Collected data were from the baseline CS diagnosis. Patients with score 36 or above were classified as highly likely to have LS. We compared the results with the liver steatosis diagnosed by abdominal ultrasonography (USG), clinical and demographic factors.

Results: 82 out of 135 patients, aged 27-87 years, predominantly women (N=64), were eligible for the study. The etiology of CS was mostly pituitary (47), followed by adrenal (20) and ectopic cause (15). 81.7% patients, showed high HSI (82.8% of females, 77.8% of males). HSI was elevated in 85, 80 and 73 percent of patients with pituitary, adrenal and ectopic CS. 41% of patients with elevated HSI were obese. HSI was elevated among: 100% patients with confirmed liver steatosis on USG, 72% patients with normal USG and 78% patients who hadn't have USG performed.

Conclusions: The prevalence of liver steatosis in active CS may be much higher than previously reported. Further investigation should be undertaken to show if patients with high risk of liver steatosis based on HSI and normal liver image on USG, may benefit from liver MRI in order to verify the diagnosis.

Abstract-ID: 129

BONE HEALTH AND SKELETAL FRAGILITY IN SECOND- AND THIRD-LINE MEDICAL THERAPIES FOR ACROMEGALY: PRELIMINARY RESULTS FROM A PILOT MONOCENTER EXPERIENCE

Sabrina Chiloiro¹, Antonella Giampietro², Amato Infante³, Pier Paolo Mattogno⁴, Martina Cicia⁵, Claudia Dell'Atti⁶, Liverana Lauretti⁴, Alessandro Olivi⁴, Laura De Marinis², Francesco Doglietto⁴, Antonio Bianchi²

¹*Department of Endocrinology, Catholic University of the Sacred Heart, Rome, Italy*

²*Pituitary Unit, Department of Endocrinology and Diabetes, Fondazione Policlinico Universitario A. Gemelli, Irccs, Rome, Italy*

³*Department of Diagnostic Imaging, Oncological Radiotherapy, and Hematology, Fondazione Policlinico Universitario A. Gemelli Irccs, Rome, Italy*

⁴*Department of Neurosurgery, Fondazione Policlinico Universitario A. Gemelli Irccs, Rome, Italy*

⁵*Dipartimento DI Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy*

⁶*Department of Diagnostic Imaging, Oncological Radiotherapy, and Hematology, Fondazione Policlinico Universitario A. Gemelli Irccs, Rome, Italy*

Introduction: Skeletal fragility is a clinically relevant and not-reversible complication of acromegaly, involving around 40% of patients at the time of acromegaly diagnosis. Few studies have investigated the effects on skeletal health of medical therapies for acromegaly.

In this retrospective longitudinal monocenter study, we investigated the outcome of skeletal fragility in patients treated with Pasireotide Lar in combination with Pegvisomant (PAS-Lar +Peg-V), also by comparison to those observed in patients treated with conventional therapies.

Results: We included 6 patients treated with PAS-Lar +Peg-V, 6 patients treated with Peg-V in monotherapy, 16 patients treated with Peg-V plus first-generation somatostatin receptor ligands (fg-SRLs), and 10 patients treated with Pasi-Lar. None of the patients treated with PAS-Lar+Peg-V experienced worsening of spine and femoral bone mineral density (BMD) and incident vertebral fractures (i-VFs). The frequency of i-VFs was significantly lower in patients treated with the Peg-v+Pasi-Lar (0%), as compared to those observed in m-Peg-V treated patients (50%, $p=0.03$). The frequency of i-VFs was slightly but not significantly higher in patients treated with Pasi-Lar (12.5% $p=0.062$) and in those treated with the fg-SRLs+Peg-V (37.5% $p=0.364$), with respect to those treated with Peg-V+Pasi-Lar (0%). I-VFs occurred more frequently in patients with a longer diagnostic delay ($p=0.047$), in patients with higher GH levels at acromegaly diagnosis ($p=0.02$), and in patients who experienced a worsening of BMD ($p=0.005$).

Conclusion: Our preliminary data suggested that in aggressive and multi-drug resistant acromegaly, the combination therapy Peg-V+Pasi-Lar may prevent the worsening of BMD and i-VFs.

Abstract-ID: 131

PD-L1 IN PITUITARY NEUROENDOCRINE TUMOURS (PITNETS): BIOLOGICAL ROLE AND THERAPEUTIC USEFULNESS

Mariana Lopes-Pinto¹, Ema Lacerda-Nobre², Ana Luísa Silva³, Pedro Marques⁴

¹Endocrinology Department, Centro Hospitalar Universitário Lisboa Norte, Lisbon Portugal, Endocrinology

²Endocrinology Department, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (Chuln), Lisbon, Portugal, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

³Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal, Instituto de Saúde Ambiental Da Faculdade de Medicina Da Universidade de Lisboa, Lisbon, Portugal

⁴Pituitary Tumor Unit, Endocrinology Department, Hospital Cuf Descobertas, Lisbon, Portugal, Faculdade de Medicina, Universidade Católica Portuguesa, Lisbon, Portugal

Background: Programmed cell death-1 (PD-1) and PD ligand-1 (PD-L1) expression predict aggressiveness and response to immune checkpoint inhibitors (ICIs) in different cancers. The expression of PD-L1 in pituitary neuroendocrine tumours (PitNETs) has been investigated in recent studies. We aimed to review the published data on PD-L1 expression in PitNETs, from the perspective of its biological role and prognostic-therapeutical usefulness in PitNET patients.

Methods: A literature review focused on studies with available data regarding PD-L1 expression in PitNETs was performed. Eight studies assessing PD-L1 positivity by immunohistochemistry (IHC) were included. Positive PD-L1 expression was considered for staining ≥ 1 -5% of tumour cells. PD-L1 positivity was then analysed based on PitNET functional status, subtype, invasion, proliferation and recurrence. Additionally, 28 case reports concerning PitNET patients who received ICIs were identified, reviewed and analysed collectively in detail.

Results: Pooled data from IHC-based studies included 807 PitNET patients, 49.9% were female, and the median age at PitNET diagnosis ranged between 45-70.5years. The cohort consisted of 434 (53.8%) non-functioning PitNETs and 373 (46.2%) functioning PitNETs: 60 growth hormone (GH)-secreting PitNETs, 69 prolactinomas, 68 adrenocorticotrophic (ACTH)-secreting PitNETs, 6 thyroid-stimulating hormone (TSH)-secreting PitNETs, and 61 plurihormonal PitNETs. PD-L1 expression was positive in 339 cases (42.0%). PD-L1 positivity was more frequent in functioning-PitNETs than NF-PitNETs (52.8% vs 32.7%; $p < 0.001$). GH-secreting PitNETs and prolactinomas had significantly higher rates of positive PD-L1 expression (56.7% and 53.6%, respectively) than other tumour subtypes. PD-L1 positivity was documented in 36.6% of invasive PitNETs and in 32.1% of non-invasive PitNETs, while a higher proportion of PD-L1 positive expression was found in proliferative PitNETs in comparison to the non-proliferative counterparts (43.3% vs 23.9%; $p < 0.001$). Primary PitNETs had positive PD-L1 expression in 21.9% of cases, while only 13% of the recurrent PitNETs showed PD-L1 positive expression.

Eighteen out of the 28 (64.3%) aggressive or metastatic PitNETs treated with PD-1 inhibitors had a positive radiological response to PD-1 inhibitors, of which 10 and 4 cases were ACTH-secreting and prolactin-secreting PitNETs, respectively. Data from a multicentric cases series showed no association between PD-L1 expression and response to ICIs (Ilie 2020 ERC).

Conclusions: PD-L1 is expressed in a significant proportion of PitNETs, predominantly in functioning tumours. Higher PD-L1 positivity rates were found in proliferative PitNETs, but not in invasive or recurrent PitNETs. Favourable response to anti-PD-1 drugs may occur in substantial number of aggressive or metastatic PitNETs, regardless the PD-L1 expression status; thus, absence of PD-L1 expression should not preclude such patients from receiving ICIs.

Abstract-ID: 137

ELEVATED HEMOGLOBIN AND HEMATOCRIT IN CUSHING'S SYNDROME PATIENTS: IMPACT OF ETIOLOGY, GENDER AND REMISSION STATUS ON ERYTHROCYTIC PROFILE

Laura Dery¹, Amit Akirov², Julia Stern¹, Ilan Shimon³, Yaron Rudman⁴, Shiri Kushnir⁵

¹*Sackler School of Medicine, Tel Aviv University, Israel*

²*Rabin Medical Center, Beilinson Campus, Petah-Tikva, Israel*

³*Institute of Endocrinology, Beilinson Hospital, Sackler School of Medicine, Tel Aviv University, Israel*

⁴*Beilinson Hospital, Rabin Medical Center, Institute of Endocrinology, Petah Tikva, Israel*

⁵*Beilinson Hospital, Rabin Medical Center, Research Authority, Petah Tikva, Israel*

Background: As glucocorticoids are known to stimulate erythropoiesis, Cushing's syndrome (CS) has various effects on hematological parameters. We aim to characterize the erythrocytic profile in patients with CS and delve further into how a patient's disease etiology, gender and remission status affect their findings.

Methods: This was a retrospective, matched cohort study using data collected from Clalit Health Services, a large healthcare provider in Israel. Erythrocytic parameters were compared between CS patients and age, sex, body mass index (BMI) and socioeconomic status-matched controls in a 1:5 ratio. Laboratory values at baseline were calculated as mean values during the year preceding CS diagnosis, and over the course of one year thereafter.

Results: The cohort included 397 CS patients and 1970 controls. The mean age at diagnosis of CS patients was 51.11±16.85 years and BMI was 31.15±7.76 kg/m². Patients had a significantly higher prevalence of comorbid conditions such as diabetes, hypertension, dyslipidemia, cardiovascular disease and malignancy ($p<0.001$). The mean number of blood tests available at baseline and a year after diagnosis was 3.8±4.9 and 4.9±4.6 in CS patients, and 2.2±3.1 and 2.5±5.5 in controls. Hemoglobin (Hb), hematocrit (Hct) and mean corpuscular volume (MCV) were higher in CS patients at baseline, with median values of Hb 13.70 (12.70-14.65) g/dL, Hct 41.64 (38.77-44.51)% and MCV 87.78 (83.77-92.00) fL, compared to 13.20 (12.30-14.10) g/dL ($p<0.0001$), 39.80 (37.30-42.70)% ($p<0.0001$) and 87.00 (83.45-90.23) fL ($p=0.0028$), respectively, in controls. These trends were observed in both genders, but with greater intensity in female patients. A year following diagnosis, the absolute changes of these parameters were significantly greater compared to controls, leading to near normalization of all values. When analyzing patients based on disease origin and remission status, it was found that patients who attained remission after one year had more comparable values of Hb and Hct to control counterparts than those with persistent/recurrent disease. Pituitary CS patients in remission had Hb 13.20 (12.33-14.30) g/dL and Hct 40.08 (37.30-42.75)%, while those with persistent disease had Hb 13.75 (13.03-14.72) g/dL ($p=0.0567$) and Hct 42.45 (39.50-44.48)% ($p=0.0049$); adrenal CS patients in remission had Hb 13.20 (12.17-14.00) g/dL and Hct 40.08 (37.65-42.30), while those with persistent disease had Hb 14.08 (12.70-14.59) g/dL ($p=NS$) and Hct 42.40 (37.80-44.88)% ($p=NS$). There was no effect of CS on mean corpuscular hemoglobin (MCH) or its concentration (MCHC).

Conclusions: Erythrocytic parameters such as Hb and Hct are higher in CS patients than controls, with near normalization of both parameters in patients who attained remission within a year. The data illustrates how erythrocytic parameters are influenced by endogenous glucocorticoid excess.

Abstract-ID: 141

REAPPRAISAL OF COLORECTAL POLYPS IN ACROMEGALY: STUDY ON PREVALENCE, RECURRENCE AND RISK FACTORS

Rosa Pirchio¹, Renata Simona Auriemma², Alice Vergura¹, Rosario Pivonello³, Annamaria Colao⁴

¹Università Federico II DI Napoli, Dipartimento DI Medicina Clinica e Chirurgia, Sezione DI Endocrinologia, Diabetologia, Andrologia e Nutrizione, Naples, Italy

²Dip DI Medicina Clinica e Chirurgia, Section of Endocrinology, Naples, Italy

³Sezione DI Endocrinologia, Università Federico II DI Napoli, Naples, Italy

⁴Dip DI Medicina Clinica e Chirurgia, Sezione DI Endocrinologia, Università Federico II DI Napoli, Naples, Italy

Context: Colorectal polyposis is a major concern in patients with acromegaly.

Objective: Investigation of colorectal polyps' prevalence and recurrence risk factors in acromegaly.

Design: Retrospective study aiming at evaluating colonoscopy findings and correlation with hormonal and metabolic parameters in acromegaly.

Methods: 171 patients referring to "Federico II" University diagnosed with acromegaly from 2000 to 2022 who underwent at least one colonoscopy.

Results: Colonoscopy was performed at diagnosis in 120 (70.2%) and after a disease duration of 10.2±5.7 years in 51 patients (29.8%). Polyps were found in 37.5% and 37.2%, respectively (p=0.975). At diagnosis, polyps were found more frequently in older (p=0.003), diabetic (p=0.01) patients, with higher number of systemic complications (p<0.001). Prevalence of polyps at diagnosis was significantly higher in patients with presumed disease onset greater than 5 years (median, p=0.04). In patients who underwent colonoscopy after the diagnosis, age at diagnosis (p=0.005), fasting glucose (p<0.001), HbA1c (p<0.001), HOMAIR (p=0.009), and number of systemic complications (p=0.004) were significantly higher in patients with than those without polyps. Overall among diabetic patients, polyps prevalence was significantly higher in patients administered with insulin than in those treated with oral antidiabetic drugs (35% vs 6.25%, p=0.04). Forty-nine patients (34.2%) underwent multiple evaluations with 10-years median of colonoscopy follow-up. Among patients with positive first colonoscopy, recurrence was present in 38.2% at last evaluation, particularly in patients with uncontrolled acromegaly (p=0.003), glucose metabolism impairment (p=0.031), metabolic syndrome (MS, p=0.004), and diabetes treated with insulin therapy (p=0.001). In patients treated with somatostatin analogs, polyps recurrence was lower than those differently treated (30.4% vs 75%, p=0.03). New onset of polyps at second evaluation was found in 24.2% of patients with first negative colonoscopy, particularly in men (p=0.006), with uncontrolled acromegaly (p=0.007), and MS (p=0.002).

Overall, six patients (3.5%) had colon cancer, diagnosed in two cases at acromegaly diagnosis and in four during the follow-up, after a mean disease duration of 15.5 years.

Conclusions: Polyps' recurrence and new onset are more frequent in patients with uncontrolled acromegaly, glucose metabolism impairment, and MS. Colonoscopy follow-up should be tailored and patients with these risk factors should undergo more frequent colonoscopy evaluations.

Abstract-ID: 145

HYPONATRIEMIA AFTER TRAUMATIC BRAIN INJURY (TBI) – CASE REPORT

Ivan Jevtic¹, Dragana Miljic², Marina Nikolic Djurovic³, Mirjana Doknic⁴, Sandra Pekic Djurdjevic⁵, Marko Stojanovic⁶, Zvezdana Jemuovic⁷, Ivana Cekic⁸, Milan Petakov⁹

¹*Clinic for Endocrinology, Diabetes and Metabolic Diseases - University Clinical Centre of Serbia, Neuroendocrinology, Belgrade, Serbia*

²*Clinic of Endocrinology, Neuroendocrine Department, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia, Belgrade, Serbia*

³*Clinical Center of Serbia, Internal Medicine, Belgrade, Serbia*

⁴*Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia, Medical Faculty, University Belgrade, Endocrinology, Belgrade, Serbia*

⁵*Clinic for Endocrinology, School of Medicine, University of Belgrade, Medical Faculty, University of Belgr, Belgrade, Serbia*

⁶*Clinic for Endocrinology, Clinical Centre of Serbia, University of Belgrade, Belgrade, Serbia*

⁷*Clinic for Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia*

⁸*Neuroendocrine Department, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia;*

⁹*Department of Neuroendocrinology, Clinic for Endocrinology, Clinical Center of Serbia & School of Medicine, University of Belgrade, Neuroendocrine Department, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia, Belgrade, Serbia*

Introduction: With this case report, we illustrate complex mechanisms of disorders of water and sodium balance after TBI and strategies and clinical approach to patient with this complex condition.

Case description: 20-year-old male patient, was admitted to ER after a fall. CT showed multiple head injuries, cerebral contusions, laminar subdural hematoma, multiple facial fractures, cranial vault and base fractures, pneumocephalus and cerebral edema. Sodium and diuresis were normal on admission, but after two days mild hyponatremia was noted (Na 132 mmol/L).

On day 6 he developed severe symptomatic hyponatremia (Na=113mmol/L) with seizures and was intubated. Planned maxillofacial surgery was postponed. Hypertonic saline 3% NaCl was administered with maximum sodium correction up to 126 mmol/L. Natriuresis was 160 mmol/L. Consulting endocrinologist suggested to evaluate pituitary function and immediately after morning sampling start stress doses of hydrocortisone (2x100mg) due to patient's serious condition.

Results of endocrine evaluation appeared unremarkable, all in reference ranges (morning cortisol 414nmol/L, FSH 1,3 IU/L, LH2,1 IU/L, testosterone 7,58 nmol/L, TSH 2,67 mIU/L, fT4 22,0 pmol/L). Hyponatremia normalized within 48h (Na=134). Two days after commencement of hydrocortisone he developed hypotonic polyuria (up to 5L/day) with compensatory polydipsia. Plasma and urine osmolality, copeptin and AVP evaluation weren't available. Arginine-vasopressin (AVP) deficiency, unmasked by hydrocortisone replacement, was suspected and desmopressin was added resulting in correction of polyuria and polydipsia.

Patient successfully underwent maxillofacial surgery, performed at the department of neurosurgery, with hydrocortisone support and was discharged two days later on phenobarbiton, hydrocortisone and desmopressin with normal sodium level. He was advised to monitor water intake and urine output. Pituitary function and visualization will be assessed in next few months.

In conclusion, our patient, who presented with TBI and severe symptomatic hyponatremia due to acute anterior pituitary dysfunction, simultaneously unmasked acute AVP deficiency after replacement with stress doses of hydrocortisone for secondary adrenal insufficiency and hyponatremia.

Abstract-ID: 146**A CASE OF PREGNANCY IN PATIENT WITH AUTOIMMUNE HYPOPHYSITIS**

Martina Cicia¹, Sabrina Chiloiro¹, Antonella Giampietro¹, Flavia Angelini¹, Tommaso Tartaglione², Flavia Costanza¹, Pier Paolo Mattogno³, Rosalinda Calandrelli⁴, Simona Gaudino², Liverana Lauretti³, Francesco Doglietto³, Laura De Marinis¹, Alfredo Pontecorvi¹, Antonio Bianchi¹

¹*Pituitary Unit, Department of Endocrinology and Metabolism, Fondazione Policlinico A. Gemelli, Irccs, 00168 Rome, Italy, Department of Translational Medicine and Surgery, Università Cattolica del Sacro Cuore, 00168 Rome, Italy*

²*Department of Translational Medicine and Surgery, Università Cattolica del Sacro Cuore, 00168 Rome, Italy, Department of Radiodiagnostic, Fondazione Policlinico Universitario A. Gemelli, Irccs, 00168 Rome, Italy*

³*Neurosurgery Unit, Department of Neurosciences, Fondazione Policlinico Universitario Agostino Gemelli, Istituto DI Ricovero e Cura A Carattere Scientifico (Irccs), Rome, Italy, Neurosurgery Unit, Department of Neurosciences, Catholic University School of Medicine, Rome, Italy*

⁴*Radiology and Neuroradiology Unit, Department of Imaging, Radiation Therapy and Hematology, Università Cattolica del Sacro Cuore*

INTRODUCTION: Hypophysitis is a rare inflammatory disease of the pituitary gland with primary etiology (lymphocytic or autoimmune) or secondary to systemic or infectious diseases and drugs. Usual presenting signs and symptoms are anterior hypopituitarism, headache, diabetes insipidus and visual field disorders. The diagnosis is based on clinical, laboratory and radiological data. MRI shows increased size of the pituitary gland and thickening of the pituitary stalk. First-line treatment is based on hormone replacement and glucocorticoids; in cases of resistance, azathioprine or mycophenolate mofetil can be used. We report the case of a 32-year-old woman suffering from autoimmune hypophysitis, diagnosed 14 years before her first pregnancy.

CASE REPORT: The patient's clinical history began in 2006, when she was sixteen, with migraines and hypoadrenal crises. When she came to our observation in September 2015, pituitary MRI detected the increase of either the gland volume and the thickness of pituitary stalk. As autoimmune hypophysitis was suspected, hormonal tests were requested, confirming isolated hypoadrenalism and an antibody panel from which the positivity of anti-pituitary antibodies emerged. Hormonal replacement therapy with hydrocortisone was prescribed. Immunosuppressive treatment was started and then switched to azathioprine and Mycophenolate Mofetil (for intolerance), obtaining an improvement in the symptoms. In July 2019 the patient referred a desire for pregnancy: hormonal tests showed a substantially stable picture and a pituitary MRI which documented a slight reduction in the previously detected increase in volume of the gland. For this reason, the multidisciplinary team did not pose any contraindications to pregnancy. Strict periodic checks were therefore examined by our Center every 3-6 months, monitoring pituitary hormones, electrolytes, blood count, blood sugar and campimetric examination.

In June 2021, the patient gave birth without complications. The child was in good clinical conditions. At the last check-up in September 2023, the patient was in good clinical condition and expressed a new desire for pregnancy: the case was discussed at the Pituitary Board, the hormonal tests were evaluated and the latest pituitary MRI documented substantially unchanged findings, so the authorization for a new pregnancy was given.

CONCLUSIONS: In our experience, autoimmune hypophysitis may not be considered a major contraindication to pregnancy, if patient is in the remission phase of the disease. A disease is recommended before the conception evaluation (though pituitary hormone test and MRI) and during the pregnancy, though close periodic checks, monitoring pituitary hormones and electrolytes and performing campimetric evaluation when clinically indicated.

Abstract-ID: 147

RELEVANCE OF USP8 MUTATIONS IN THE PATHOGENESIS OF FUNCTIONING CORTICOTROPH TUMOURSMiguel Garcia¹, Araceli García-Martínez¹, Johana Sottile², Luis Valor³, Victoria González³, Lucía Martínez⁴, Javier Abarca⁵, Raúl Luque⁶, ANTONIO PICO⁷, Johana Sottile⁸¹Instituto Maimónides de Investigación Biomédica de Córdoba, Physiology, Córdoba, Spain²Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Endocrinology & Metabolism, Alicante, Spain³Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Alicante, Spain⁴Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Hospital General Universitario Dr. Balmis, Pathology, Alicante, Spain⁵Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Hospital General Universitario Dr. Balmis, Alicante, Neurosurgery, Alicante, Spain⁶Instituto Maimónides de Investigación Biomédica de Córdoba Su Ubicación Es Córdoba, Physiology, Córdoba, Spain⁷University Miguel Hernandez, Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Endocrinology & Metabolism, Alicante, Spain⁸Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Hospital General Universitario Dr. Balmis, Endocrinología Y Metabolismo, Alicante, Spain

USP8 mutations are well-known driver mutations in functioning corticotroph tumours. The study aimed to quantify the effect of USP8 mutations on clinical parameters and the expression of major genes involved in the functioning and proliferation of corticotroph tumours. Methods: We performed Sanger sequencing in 13 functioning corticotroph tumours (SCT) coming from a unique PTCOE. We retrieved demographic and clinical variables (maximum tumour diameter, invasion, and proliferation) and analysed the expression of genes (qPCR) involved in the processing of ACTH (POMC, CHRH, AVPR1, TBX19, PCSK173, PCSK 2, PAM, CPE), in ACTH secretion (CABLES1, USP8, EGFR), in the glucocorticoid receptor (GR) activity (HSF1, AP-1) and the immune microenvironment (MSH6, PDL-1). Results: four (30,8 %) tumours presented somatic USP8 mutations. In all cases, the mutations were heterozygous and were located in the exon 14 of the USP gene. All patients with mutated tumours were women vs. 55% in non-mutated tumours. Mutated tumours were smaller (DMT mean 6.75 vs. 15.89 mm (NS)) and less invasive (25 % vs. 33.3 %) than non-mutated ones and appeared in younger patients (mean 42.75 vs. 48 years; (NS)). Mutated tumours were more proliferative (Ki-67 mean 2.48 vs 0.81 %; p 0.12). In addition, mutated tumours showed higher expression of the genes involved in the processing and secretion of ACTH (POMC, CHRH, AVPR1, TBX19; USB, CABLES 1, EGFR, although only PCSK 1/3 showed statistical significance (median FC 8.2 vs. 0.91, p=0.049). Contrarily, non-mutated tumours showed higher levels of PCSK 2 (mean FC 1.08 vs 0.18; p=0.21). There were no differences in the GR pathway (HSF1 (mean FC 0.57 vs. 0.69; p=0.21); AP-1 (mean FC 0.29 vs. 0.80, p=0.16)) nor in the immune microenvironment: PDL-1 (mean FC 1.87 vs. 2.05, p=0.79) and MSH6, (mean FC 1.71 vs. 1.29; p=0.45, respectively). Contrarily, mutated tumours expressed more SSTR2 and SSTR5 than non-mutated ones (mean FC SSTR2 0.38 vs 0.12; p=0.07; median FC SSTR5 0.21 vs 0.003, p=0.006, respectively). Conclusions: The percentage of USP8 mutated functioning corticotroph tumours is low but these tumours show a higher ACTH activity through a higher POMC processing. In addition, the activity of mutated USP8 corticotroph tumours seems to be related to higher processing of POMC without differences in the negative feedback of glucocorticoid receptor. In addition, its important expression of SSTR, especially SSTR5 opens interesting medical treatment opportunities in these tumours

Abstract-ID: 151

B-RAF AND MEK INHIBITOR TARGETED THERAPY IN PAPILLARY CRANIOPHARYNGIOMAS: PRELIMINARY FINDINGS FROM A FRENCH MULTICENTER STUDY

Dario De Alcubierre¹, Grigorios Gkasdaris², Fabien Almairac³, Bertrand Baussart⁴, Julien Boetto⁵, Margaux Mordrel⁶, MOULY Céline⁷, Gérald Raverot⁸, Emmanuel Jouanneau²

¹*Sapienza University of Rome, Department of Experimental Medicine, Rome, Italy*

²*"Groupement Hospitalier Est" Hospices Civils de Lyon, Neurosurgery Department, Reference Center for Rare Pituitary Diseases Hypo, Bron, France*

³*Chu de Nice, Service de Neurochirurgie, Nice, France*

⁴*La Pitié-Salpêtrière University Hospital, Assistance Publique-Hôpitaux de Paris, Department of Neurosurgery, Paris, France*

⁵*Gui de Chauliac Hospital, Montpellier University Hospital Center, Department of Neurosurgery, Montpellier, France*

⁶*Université de Poitiers, Chu de Poitiers, Prodicet, Service D'oncologie Médicale Chu de Poitiers, Poitiers, France*

⁷*Department of Endocrinology and Metabolic Diseases, Chu Larrey, Toulouse, France*

⁸*Groupement Hospitalier Est, Inserm U1052,, Lyon I University Université de Lyon, Lyon, France*

Background: Papillary craniopharyngiomas (PCPs) are driven by V600E BRAF mutations in 95% of cases. Recently, adjuvant anti-BRAF/MEK targeted therapy (TT) has emerged as a potential treatment in aggressive PCPs. Neoadjuvant TT, aiming to shrink large, unresectable tumors before surgical removal, has also been proposed. However, standardized data on large cohorts are still lacking. Our study aimed to assess the real-life efficacy and safety of neoadjuvant and adjuvant TT in patients with PCPs.

Methods: This was a retrospective, multicenter study involving patients with V600E BRAF-mutated PCPs treated with anti-BRAF/MEK TT in France up to July 2023.

Volumetric magnetic resonance imaging analysis, clinical and hormonal assessments were performed before TT, after 3 months, and at the last available follow-up during treatment.

Radiological response was classified as either complete (lesion disappearance), subtotal (volume reduction > 90%), partial (volume decrease 30-90%), stable disease (volume decrease < 30% or increase < 20%), or progressive disease (volume increase > 20%).

Results: Eleven patients [4 females, mean age 48.5±16.7 years] were included. Patients received either neoadjuvant therapy (NA) for non-resectable tumors (n=3), adjuvant therapy (AD) post-surgery (n=6), or palliative therapy (PA) for recurrent or residual tumors despite multimodal treatment (n=2).

Prior to TT initiation, symptoms included headache (5 patients), endocrine dysfunction (10), visual impairment (8), weight gain (2), and neurological derangements (3). Median tumor volume was 3777 cm³ [1507-42605].

All patients underwent combined anti-BRAF/MEK therapy for a mean duration of 8.7±6.1 months.

After 3 months, median volume reduction was 81.1% [49.7-91.7], 55.5% [20.0-78.9], and 60.8% [43.5-78.1] in the NA, AD, and PA groups, respectively.

At the last follow-up, six patients (3 NA, 2 AD, 1 PA) showed subtotal response, four (3 AD, 1 PA) exhibited partial response, and one AD patient maintained stable disease. Median volume reduction was 91.7% [91.4-92.7] in the NA group, 79.2% [20.0-93.2] in AD patients, and 91.8% [88.6-94.8] in the PA group.

Clinically, TT resolved headaches and visual impairment in 4 and 7 patients, respectively. Two patients had improved neurological symptoms and one presented weight loss, but none recovered endocrine function.

Three patients experienced treatment-related adverse events. Two developed hepatic cytolysis, leading to temporary TT discontinuation and later reintroduction. One patient permanently discontinued TT due to vomiting, asthenia, skin rash, urinary tract infections, and hyperthermia.

Conclusions: Targeted therapy in PCP patients can induce tumor volume reduction and clinical improvement within a few months from treatment initiation. However, adverse events warrant careful monitoring. Further research is needed to establish standardized protocols and confirm these findings on larger cohorts.

Abstract-ID: 152

GENDER SPECIFIC EFFECT OF FGF21 IN THE RECOVERY OF THE HYPOTHALAMIC-ADRENAL AXIS AFTER CUSHING SYNDROME.

Daniela Diaz¹, Julia Capo², Arturo Vega-Beyhart³, Maite Rodrigo⁴, Gregori Casals⁵, Felicia Alexandra Hanzu⁶

¹Hospital Clinic Barcelona, Idibaps, Group of Endocrine Disorders, Barcelona, Spain

²Hospital Clinic, Idibaps, Group of Endocrine Disorders, Barcelona, Spain

³Hospital Clinic Barcelona/Idibaps, Hospital Ramon Y Cajal Madrid, Endocrinology, Barcelona, Spain

⁴Hospital Clinic Barcelona, Anatomopatology Department, Spain

⁵Biochemistry and Molecular Genetics Service, Hospital Clínic de Barcelona,, Centro de Investigación Biomédica En Red de Enfermedades Hepáticas Y Digestivas (Ciberehd), Institut D'investigacions Biomèdiques August Pi I Sunyer (Idibaps), Barcelona, Spain

⁶Hospital Clinic Barcelona, Idibaps/University Barcelona, Endocrinology/ Group of Endocrine Disorders, Barcelona, Spain

Long-term glucocorticoid (GC) treatment is associated with a high burden of cardiovascular disease and metabolic disorders, such as Cushing's syndrome (CS). After CS is treated, patients present chronic adrenal insufficiency (AI), hypothalamus-pituitary-adrenal (HPA) axis dysfunction, and a persistent metabolic syndrome feature. Fibroblast growth factor (FGF) -21, a key regulator of metabolism, has a bidirectional relationship with GC that bypasses the negative feedback of the HPA axis. In this study, we aimed to investigate the potential effects of FGF21 in a transgenic mouse model that overexpresses FGF21 (Fgf21-Tg) during a 5-week chronic hypercortisolism (CORT) treatment with 1mg/mL corticosterone CORT (active CS) and after a 10-week CORT withdrawal (recovery phase), we treated Fgf21-Tg and wild-type (WT) male and female mice with CORT or vehicle (VEH) in drinking water. We used immunoassay to assess plasma circadian CORT and ACTH levels and analyzed gene expression from the adrenal, hypothalamus, and pituitary by qPCR. Finally, we collected all the samples during the waking circadian mice cycle (PM).

During active CS, WT male and female CORT-treated mice exhibited lower fasting plasma glucose than their respective VEH groups due to basal hyperinsulinemia. On the contrary, there were no differences in fasting plasma glucose and insulin levels between the Fgf21-Tg male and female mice. Interestingly, in the CORT-treated male mice, the Fgf21-Tg group had higher CORT and ACTH plasma levels than the WT group during the active phase. In the same line, we observed that treated Fgf21-Tg male mice had higher hypothalamic *Crh* and pituitary *Pomc* gene expression levels compared with the CORT-WT male mice. Moreover, Fgf21-Tg female mice CORT-treated had higher CORT plasma levels and hypothalamic *Crh* expression levels than the WT group during the active phase. Fgf21-Tg male and female groups CORT-treated presented lower *Mc2r* adrenal expression levels than their corresponding CORT-WT groups. In the recovery phase, CORT-Fgf21-Tg male and female mice maintain higher CORT plasma levels, similar ACTH plasma levels, and higher *Cyp11b1* adrenal expression levels than their respective CORT-WT groups.

Our data describe that during chronic hypercortisolism, FGF21 contributes to maintaining a sustained HPA axis and suggests that a possible treatment with higher doses of FGF21 may support adrenal renewal since after the GC-chronic treatment results in higher CORT secretion.

Abstract-ID: 155

CLINICAL CHARACTERISATION OF RADIOLOGICALLY INVASIVE SOMATOTROPH PITUITARY NEUROENDOCRINE TUMOURS

Luis Cardoso¹, Ana Carreira², Mafalda Ferreira², Daniela Guelho², Mariana Lavrador², Inês Vieira², João Vinagre³, Arnaud Cruz Paula³, João Almeida⁴, José Manuel Lopes⁵, Gonçalo Guerreiro Costa⁶, Olinda Rebelo⁷, Paula Soares³, Leonor Gomes⁸, Isabel Paiva²

¹Coimbra Hospital and University Centre, I3s - Institute for Research and Innovation in Health of the University of Porto, Department of Endocrinology, Diabetes and Metabolism, Coimbra, Portugal

²Department of Endocrinology, Diabetes and Metabolism, Coimbra Hospital and University Centre, Portugal

³Ipatimup - Institute of Molecular Pathology and Immunology of the University of Porto, I3s - Institute for Research and Innovation in Health of the University of Porto, Portugal

⁴Department of Anatomic Pathology, São João University Hospital Center, Portugal

⁵Department of Anatomic Pathology, São João University Hospital Center, I3s - Institute for Research and Innovation in Health of the University of Porto, Portugal

⁶Department of Neurosurgery, Coimbra Hospital and University Centre, Portugal

⁷Department of Anatomic Pathology, Coimbra Hospital and University Centre, Portugal

⁸Department of Endocrinology, Diabetes and Metabolism, Coimbra Hospital and University Centre, Faculty of Medicine of the University of Coimbra, Portugal

Pituitary neuroendocrine tumours, particularly somatotroph tumours (STs), are often benign, but a subset exhibits invasive behaviour, causing significant morbidity and posing treatment challenges. This study aimed to characterize invasive STs, shedding light on clinical and pathological behaviour.

We retrospectively studied 75 patients with STs recruited at the outpatient clinic. Most patients (n=50; 66.7%) were females; mean age at diagnosis of 48±13 years old; approximately 70% patients were diagnosed in the last 13 years (minimum 1988, maximum 2021); at diagnosis, mean GH and IGF1 were 36.09±96.90 and 2.83±1.51 times the upper limit of normal (ULN), respectively.

Imaging data on invasiveness, at diagnosis, was available for most patients (n=60/75, 80%) and half (n=30) of patients had cavernous or sphenoidal sinus invasion. Patients with invasive STs were younger 44.87±11.35 vs 50.73±14.79 years old, but not statistically significant. Invasive tumours were significantly larger (median 25.5 [18-35.7] vs 17.2 [12-21] mm, p=0.009). GH (10.50 vs 5.05 times ULN) and IGF1 (3.23 vs 2.60 times ULN) levels, at diagnosis, were higher in the invasive group, but not statistically significant. Preoperative hypopituitarism was similar between both groups, but adrenal failure was only reported in patients with invasive tumours (n=4). Apparent complete resection was less frequent in patients with invasive tumours (37% vs 55.6%), though not significant, and was significantly less frequent in patients with suprasellar extension (OR 0.2 [0.06-0.66], p=0.008). Postoperative remission was significantly lower 17.9% (vs 53.6%, p=0.005) in patients with invasive tumours. Imaging and biochemical remission at first year followed the same trend, and was lower in invasive tumours: 10.3% (vs 46.4%, p=0.002) and 22.2% (vs 55.6%, p=0.012), respectively. The number of reinterventions was similar in patients with invasive (16.7%) and non-invasive (23.3%) tumours. Immunohistochemical staining of GH-only, or co-staining of other hormones (prolactin, TSH, LH or FSH), or Ki-67 were not associated with invasiveness of STs. At study inclusion, 79.3% (vs 40.7%, p=0.003) of patients with invasive STs had persistent disease, requiring medical therapy, with similar biochemical responses (72.7% vs 60.0%, respectively, p=0.748).

In conclusion, our study revealed that patients with invasive STs are often diagnosed with larger tumours, highlighting the aggressive nature of this subset, and the suprasellar extension was a significant determinant for a successful complete resection. GH and IGF1 levels, at diagnosis, and hormonal staining were not associated with an invasive behaviour on imaging. Finally, the majority of patients with invasive somatotroph tumours experience persistent disease necessitating medical therapy. This underscores the ongoing imperative to gain a deeper comprehension of these tumours, with a particular emphasis on elucidating the molecular mechanisms underlying their invasiveness.

Abstract-ID: 157

HYPONATREMIA IN A SPECIALIZED ENDOCRINE UNIT: ENDOCRINE VS NON-ENDOCRINE CAUSES, COMPARISON OF CLINICAL COURSE AND PRESENTATION

Sanja Borozan¹, Marina Nikolic Djurovic², Mirjana Doknic³, Sandra Pekic Djurdjevic⁴, Marko Stojanovic⁵, Zvezdana Jemuovic⁶, Ivana Cekic⁷, Ivan Jevtic⁸, Dragana Miljic⁹, Milan Petakov¹⁰

¹Clinical Center of Montenegro, Department of Endocrinology, Podgorica, Montenegro

²Clinical Center of Serbia, Internal Medicine, Belgrade, Serbia

³Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia, Medical Faculty, University Belgrade, Endocrinology, Belgrade, Serbia

⁴Clinic for Endocrinology, School of Medicine, University of Belgrade, Medical Faculty, University of Belgr, Belgrade, Serbia

⁵Clinic for Endocrinology, Clinical Centre of Serbia, University of Belgrade, Belgrade, Serbia

⁶Clinic for Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia

⁷Neuroendocrine Department, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia;

⁸Clinic for Endocrinology, Diabetes and Metabolic Diseases - University Clinical Centre of Serbia, Neuroendocrinology, Belgrade, Serbia

⁹Clinic of Endocrinology, Neuroendocrine Department, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia, Belgrade, Serbia

¹⁰Department of Neuroendocrinology, Clinic for Endocrinology, Clinical Center of Serbia & School of Medicine, University of Belgrade, Neuroendocrine Department, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia, Belgrade, Serbia

Introduction:

The aim of this study was to compare clinical course and presentation in patients with endocrine (ENhypoNa) and non-endocrine (NEhypoNa) causes of hyponatremia.

Patients and methods:

Fifty-two patients with hyponatremia ($\text{Na} < 135 \text{ nmol/l}$) were referred to Department of Neuroendocrinology, University Clinical Center of Serbia from January 2015 to March 2023 (N=52; 31 females, 60 %) mean age 60.5 ± 14.1 years, mean serum sodium level $124.9 \pm 9.0 \text{ mmol/l}$. Seven patients (13.4%) with translocational hyponatremia, caused by hyperglycemia were excluded from the analysis.

Results:

In the NEhypoNa group (n=27, 60%), syndrome of inappropriate antidiuresis (SIAD) was the leading cause diagnosed in 17 patients (37.9%); caused by a malignancy in almost half of them. Other causes of non-endocrine hyponatremia were primary polydipsia, multiple mechanisms and hypervolemia, while in 3 patients (11%) the etiology remained unknown.

In ENhypoNa group (n=18, 40%), secondary adrenal insufficiency (sAI) was diagnosed in 12 (26.7%) and primary adrenal insufficiency (pAI) in 6 (13.3%) of patients. In 2/3 of patients hyponatremia led to diagnosis of previously unrecognized AI and hypopituitarism.

No significant differences between the groups in age, gender, body mass index or smoking habits were detected. Patients with ENhypoNa more frequently presented with acute hyponatremia (s $\text{Na} < 124 \text{ mmol/l}$; 77.8% vs 25.9%) and more severe symptoms (77.7% vs 37%; $p=0.05$), although mean serum Na ($122.8 \text{ vs } 124.4 \text{ mmol/l}$; $p= 0.583$) and duration of hospitalization were not significantly different ($27.8 \pm 17.1 \text{ vs } 26.7 \pm 17.6 \text{ days}$; $p= 0.844$). On discharge, patients with non-endocrine causes had significantly lower serum sodium levels compared to patients with endocrine causes, resulting in lower rate of sodium normalization ($p=0.009$).

Conclusion:

Unrecognized (secondary) adrenal insufficiency, was the leading cause of hyponatremia in our endocrine unit. These patients presented with more severe hyponatremia and symptomatology, but recovered fully after hydrocortisone stress dose replacement, compared to patients with non-endocrine causes, who presented less frequently with severe and symptomatic hyponatremia, but more frequently failed to completely normalize serum sodium levels during hospitalization.

Abstract-ID: 158

FACTORS INFLUENCING THE TARGET DOSE OF STEROIDOGENESIS INHIBITORS IN THE TREATMENT OF CUSHING'S SYNDROME - A REAL LIFE PERSPECTIVE

Juliana Gonçalves¹, Telma Moreno², Helena Urbano Ferreira³, Davide Carvalho⁴, Sandra Belo⁵, Jorge Pedro⁶, Joana Queirós⁷

¹Associação Dos Amigos Do Serviço de Endocrinologia Do Hospital de S. João, Faculty of Medicine of University of Porto, Department of Endocrinology, Matosinhos, Portugal

²Centro Hospitalar Universitário de São João, Medicine Faculty of University of Porto, Department of Endocrinology, Diabetes and Metabolism, Porto, Portugal

³Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo, Medicine Faculty of University of Porto, Centro Hospitalar Universitário São João, Serviço de Endocrinologia Diabetes e Metabolismo, Lisboa, Portugal

⁴Chus João, Faculty of Medicine, I3s University of Porto, Porto, Portugal

⁵Centro Hospitalar Universitário de São João, Department of Endocrinology, Diabetes and Metabolism, Porto, Portugal

⁶Centro Hospitalar Universitario Sao, Medicine Faculty of University of Porto, Endocrinology, Porto, Portugal

⁷Centro Hospitalar Universitário de São João, Department of Endocrinology, Diabetes and Metabolism,, Porto, Portugal

Introduction: Ketoconazole and metyrapone are steroidogenesis inhibitors used as first- or second-line treatment of hypercortisolism. The dose of these drugs can be titrated based on serum cortisol and urine cortisol excretion levels. The target urine cortisol value typically falls within the mid-range to slightly above the upper limit of the reference range. In many laboratories, the measurement of 24h urinary free cortisol (24h-UFC) is a long-standing practice, which may not allow a rapid dose adjustments.

Objective: To identify potential predictors of target dose for steroidogenesis inhibitors in a population diagnosed with Cushing's Syndrome (CS).

Methods: Retrospective study of patients with CS treated with ketoconazole or metyrapone from January 2007 to July 2023 in a Portuguese tertiary hospital. Patients who did not achieve biochemical control were excluded. The 24h-UFC within the reference range was considered as the target for biochemical control. Linear regression was used to identify predictors of the target dose for steroidogenesis inhibitors. The potential predictors tested included demographic data, anthropometry, CS type, previous treatment, block and replace regimen, arterial blood pressure, and biochemical parameters.

Results: Thirty-four patients were included: 21 treated with ketoconazole, and 13 with metyrapone. Among these patients, 26 (76.5%) had Cushing Disease, four (11.8%) had Ectopic CS, and four (11.8%) were diagnosed with Primary Bilateral Macronodular Adrenal Hyperplasia. Most patients, 28 of 34 (82.4%), were female, and the median age was 45.5 (15.5-75.5) years. At diagnosis, the median 24h-UFC was 398.8 (p25-75 168-955)µg/24h; [ref: 26-137], the median midnight salivary cortisol was 0.690 (p25-75 0.559-1.771)µg/dL; [ref: <0.320], and the median cortisol after overnight dexamethasone suppression test was 16.5 (p25-74 11.2-30.5)µg/dL [ref: <1.8]. Upon achieving biochemical control, the median [range] daily dose of ketoconazole and metyrapone was 400 [200 to 1000]mg and 1000 [500 to 3000]mg, respectively. The average 24h-UFC level was 61.5±33.9µg/24h, and the median morning cortisol was 13.6 (2.10-25.1)µg/dL. Midnight salivary cortisol ($\beta=0.723$, 95%CI[0.031-1.415], $p=0.042$), total cholesterol ($\beta=0.016$, 95%CI[0.001-0.031], $p=0.033$), and diastolic arterial blood pressure ($\beta=0.046$ 95%CI [0.003-0.088], $p=0.036$) before medical treatment showed a positive association with the prescribed dose of steroidogenesis inhibitors.

Conclusion: Despite the small sample size, these findings suggest that midnight salivary cortisol levels, total cholesterol level, and diastolic arterial blood pressure at diagnosis may be associated with the required dosage of steroidogenesis inhibitors in the treatment of patients with CS. Further multicentre studies with a larger sample size are necessary to clarify these questions.

Abstract-ID: 159

FLUORESCENCE DETECTION OF PITUITARY NEUROENDOCRINE TUMOUR DURING ENDOSCOPIC TRANSPHENOIDAL SURGERY USING BEVACIZUMAB-800CW: A QUANTITATIVE DOSE-FINDING TRIAL (DEPARTURE TRIAL).

Iris Schmidt¹, Rob Vergeer², Mark Postma³, Gerrit van den Berg³, van der Klauw MM³, Andrea Sterkenburg¹, Astrid Korsten-Meijer⁴, Robert Feijen⁴, Schelto Kruijff⁵, Andre van Beek³, Wilfred den Dunnen⁶, Dominic Robinson⁷, Marc van Dijk², Wouter Nagengast¹, Jos Kuijlen²

¹ Department of Gastroenterology and Hepatology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

² Department of Neurosurgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

³ Department of Endocrinology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

⁴ Department of Otorhinolaryngology – Head and Neck Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

⁵ Department of Surgical Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

⁶ Department of Pathology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

⁷ Center for Optical Diagnostics and Therapy, Department of Otorhinolaryngology – Head and Neck Surgery, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Background – achieving endocrine remission by gross total resection is challenging in pituitary neuroendocrine tumours (PitNETs) with cavernous sinus invasion. This study aims to assess the safety, feasibility, and dose-escalation of intraoperative fluorescence imaging as an added instrument to discriminate PitNET from surrounding tissue using bevacizumab-800CW, targeting vascular endothelial growth factor A (VEGF-A).

Methods – In part I, dose-escalation (0-4.5-10-25 mg) was performed in 4 groups of 3 patients with PitNET Knosp grade 3-4. In part II, after interim analysis, the 10 mg and 25 mg groups were expanded to a total of 6 patients. Quantitative fluorescence molecular endoscopy consisted of wide field fluorescence molecular endoscopy and multi-diameter single fiber reflectance / single fiber fluorescence spectroscopy. Mean fluorescence intensity (MFI) of the fresh surgical specimen was calculated and VEGF-staining was performed.

Findings – Eighteen patients were included. All doses were well tolerated. Three serious adverse events were registered, but none were tracer-related. Part I showed an adequate in-vivo tumour-to-background ratio for both 10 mg (TBR 2.02, $p=0.0095$) and 25 mg (TBR 2.18, $p=0.1$). Part II revealed a substantially higher MFI in the 25 mg group. With both 10 mg and 25 mg a significant difference between tumour and surrounding tissue was detected ($p < 0.0001$). All surgical specimens had VEGF-A expression.

Interpretation – This study demonstrates the safety and feasibility of quantitative fluorescence molecular endoscopy during PitNET surgery. Both 10 mg and 25 mg bevacizumab results in clear differentiation in-vivo, with improved contrast ex-vivo (MFI) in the 25mg group. Quantitative fluorescence molecular endoscopy with bevacizumab-800CW has the potential to improve gross total resection in PitNETs with cavernous sinus invasion.

Abstract-ID: 161

PSYCHOPATHOLOGICAL CHARACTERISTICS IN PATIENTS WITH ARGININE VASOPRESSIN DEFICIENCY (CENTRAL DIABETES INSIPIDUS) AND PRIMARY POLYDIPSIA COMPARED TO HEALTHY CONTROLS

Julia Beck¹, Cihan Atila², Julie Refardt³, Zoran Erlic⁴, Juliana B Drummond⁵, Clara O Sailer², Matthias Liechti², Beatriz Santana Soares Rocha⁶, Felix Beuschlein⁴, Bettina Winzeler², Mirjam Christ-Chrain²

¹University Hospital Basel, Endocrinology, Basel, Switzerland

²University Hospital Basel, Switzerland

³Erasmus Medical Center, Erasmus Medical Center, Rotterdam, Netherlands

⁴University Hospital Zürich, Switzerland

⁵Medical School of the Federal University of Minas Gerais, Belo Horizonte, Brazil

⁶Medical School of the Federal University of Minas Gerais, Brazil

The differential diagnosis between arginine vasopressin deficiency (AVP-D), known as central diabetes insipidus, and primary polydipsia (PP) is challenging. Psychopathologic findings are often used as a hallmark for diagnosing PP; thus. Yet, psychopathologic characteristics are barely assessed in patients with AVP-D, and to date, no data exist comparing AVP-D and PP with regard to these features. Therefore, in this study, we aimed to compare levels of anxiety, depression, alexithymia, and overall mental health in patients with AVP-D and PP.

In total, 82 participants (n=39 with AVP-D, n=28 with PP, and n=15 healthy controls [HC]) underwent a psychological evaluation with standardized questionnaires. Anxiety levels were assessed using the State-Trait Anxiety Inventory, mood using the Beck's Depression Inventory, alexithymia using the Toronto Alexithymia Scale, and overall physical and mental health using the Short Form 36 Health Survey (SF-36). Higher STAI, BDI, and TAS scores indicate higher anxiety, depression, and alexithymia levels. Higher SF-36 scores indicate better health and less disability.

Compared with HC, patients with AVP-D and PP showed increased levels of anxiety (HC 28 points [24, 31] vs. AVP-D 36 points [31, 45], $p<0.01$; vs. PP 38 points [33, 46], $p<0.01$), depression (HC one point [0, 2] vs. AVP-D 7 points [4, 14], $p<0.01$; vs. PP 7 points [3, 13], $p<0.01$), and alexithymia (HC 30 points [29, 37] vs. AVP-D 43 points [35, 54], $p<0.01$; vs. PP 46 points [37, 55], $p<0.01$). Levels of anxiety, depression, and alexithymia showed no difference between patients with AVP-D and PP ($p=0.58$, $p=0.90$, $p=0.50$).

This is the first study demonstrating comparable increased levels of anxiety, depression, alexithymia, and overall reduced mental health in patients with AVP-D and PP. Based on these data, psychopathological findings should not be used as a hallmark to differentiate between both conditions.

Abstract-ID: 165

PAM EXPRESSION IN PITUITARY NEUROENDOCRINE TUMORS (PITNETS)

Maria Francesca Birtolo¹, Bertrand Baussart², Nesrine Benanteur³, Anne Jouinot⁴, Adrian Daly⁵, Andrea Lania⁶, Jerome Bertherat⁴, Constantine Stratakis⁷, Guillaume Assié⁴, Giampaolo Trivellin⁸, Chiara Villa⁹

¹Université Paris Cité, Cnrs Umr8104, Inserm U1016, Institut Cochin, Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20090, Pieve Emanuele, MI, Italy., France

²Institut Cochin (Inserm U1016), Paris, France, Department of Neurosurgery, Hôpital Universitaire Pitié-Salpêtrière, Aphp, Sorbonne Université, Paris, France, France

³Institut Cochin (Inserm U1016), Paris, France, France

⁴Institut Cochin (Inserm U1016), Paris, France, Département Endocrinologie, Métabolisme Et Cancer, Chu Cochin, Institut Cochin, Inserm Cnrs, Université de Paris, France

⁵Department of Endocrinology, Centre Hospitalier Universitaire de Liège, University of Liège, Domaine Universitaire du Sart-Tilman, 4000 Liège, Belgium, Belgium

⁶Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20090, Pieve Emanuele, MI, Italy., Endocrinology, Diabetology and Andrology Unit, Irccs Humanitas Research Hospital, Rozzano, MI, Italy., Italy

⁷Human Genetics & Precision Medicine, Imbb, Forth, Heraklion, Greece & Nih, Bethesda, MD, USA, Greece

⁸Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20090, Pieve Emanuele, MI, Italy., Italy

⁹Institut Cochin (Inserm U1016), Paris, France, Department of Neuropathology, Hôpital Universitaire Pitié-Salpêtrière, Aphp, Sorbonne Université, Paris, France, France

PAM encodes a multifunctional protein recognized as an important regulator of hormone amidation and secretion. Since *PAM* germline mutations have been recently identified in patients with PitNETs, it has been proposed as a candidate gene associated with pituitary hypersecretion.

Aim: To characterize *PAM* expression in a large cohort of PitNETs through immunohistochemistry and transcriptome analysis (RNA sequencing).

Methods: Immunohistochemistry analysis was performed on 5 normal pituitary and 102 PitNET FFPE samples, including all histotypes (16 functioning and 13 silent corticotrophs, 19 somatotrophs, 20 gonadotrophs, 8 null-cell, 19 prolactinomas, and 7 thyrotrophs). *PAM* immunoreactivity was graded considering the percentage of positive cells and the staining intensity (scored from 0 to 3). The final score was obtained as follow: score = (%x0)+(x1)+(x2)+(x3). *PAM* expression was assessed through transcriptome analysis on a sub cohort of 49 PitNETs in a previously reported dataset (Neou M, ..., Assié G. *Cancer Cell*. 2020).

Results: *PAM* immunostaining was positive almost in all samples with variable patterns of expression. However, the immunohistochemistry score was lower in corticotroph tumors with overt Cushing disease compared to the other groups ($p = 1.006e-06$). Transcriptome analysis performed on a sub cohort confirmed this finding ($p = 0.020$). Interestingly, we found weak and negative staining for *PAM* in 5 patients (2 acromegalic and 3 with overt Cushing disease) in whom *PAM* variants have recently been identified (Trivellin G, ..., Stratakis CA. *Front Endocrinol*. 2023).

Conclusion: Our preliminary results add to the characterization of *PAM* function in PitNETs. A reduced expression in corticotroph PitNETs with overt Cushing disease opens new insights into the pathogenesis of -and secretion by- corticotroph tumor cells.

Abstract-ID: 170**INFLUENCE OF HYPERPROLACTINEMIA ON IMMUNOHISTOCHEMICAL AND MORPHOLOGICAL CHARACTERISTICS OF BREAST CANCER**Aliya Gumarova¹, Zamira Khalimova²¹*Republican Specialized Scientific and Practical Medical Center of Endocrinology Uzbekistan, Tashkent, Uzbekistan*²*Republican Specialized Scientific-Practical Medical Center of Endocrinology, Republican Center of Endocrinology, Republican Center of Endocrinology, Tashkent, Uzbekistan*

The study included 100 female patients with breast cancer associated with hyperprolactinemia. To achieve the set objective, all patients were divided into two groups: Group I - 70 women with hyperprolactinemia associated with breast cancer, and Group II - 30 patients with breast cancer and normal prolactin levels. Hormonal status was evaluated by measuring prolactin, estradiol, luteinizing hormone, follicle-stimulating hormone, progesterone, testosterone, thyrotropin, and free thyroxine levels using immunochemiluminescent assays. Histological status was determined for all patients through core biopsies, aspiration and incisional biopsies of the breast, and immunohistochemical (IHC) examination, with the expression of ER, PR, HER-2, and Ki-67 receptors being determined. Imaging methods included ultrasound examination of the breasts, mammography, and whole-body magnetic resonance imaging (MRI) to detect pituitary adenomas, neoplasms, and the presence of metastases. The inclusion criteria for the study were as follows: women with elevated prolactin levels above 23.3 ng/mL in at least two measurements, confirmed breast cancer, age of the patient between 19 and 65 years. The exclusion criteria included the presence of concomitant endocrine disorders such as hypothyroidism, thyrotoxicosis, type 1 and 2 diabetes, cessation of breastfeeding at least 2 years before the study, stage III breast cancer, liver cirrhosis, and medication use (dopamine agonists, psychotropic drugs, etc.) within a month before the study. Comparative study of the immunohistochemical characteristics of the receptor status in breast cancer tissue in the investigated groups revealed a significant increase in HER2/neu (67.2%) and Ki-67 (52.7%) in Group I compared to (9.9%) and (9.6%) respectively in Group II ($p < 0.001$). Estrogen receptors (ER) and progesterone receptors (PR) predominated significantly in women of Group II, with 81.6% and 59.6%, respectively, compared to 24.8% and 19.3% in Group I ($p < 0.001$). These findings suggest that in cases of normal prolactin levels, breast cancer is highly differentiated with low proliferative activity and minimal aggressive progression. The study of the immunohistochemical characteristics of the receptor status of breast tissue, taking into account the prolactin level and molecular subtype of the tumor, revealed a predominance of triple-negative subtype in 32.9% compared to 3.3%, as well as non-luminal subtype in 20% compared to 3.3% in Group I. Conversely, in Group II, the majority of cases were luminal A in 73.3% compared to 14.3% of molecular subtypes ($p < 0.001$). Ki-67 ($r = 0.6$), HER2/neu ($r = 0.7$), metastasis ($r = 0.56$), estradiol (0.63), and invasive ductal carcinoma ($r = 0.6$) and adenocarcinoma ($r = 0.5$), while showing a negative correlation with ER (-0.67) and PR (-0.59), as well as papillary carcinoma ($r = -0.78$), in situ ductal carcinoma ($r = -0.69$), and in situ intraductal carcinoma ($r = -0.65$) respectively, with a significance of $p = 0.001$.

Abstract-ID: 173

COMPARISON OF PLASMA CORTISOL CUT-OFFS USING IMMUNOASSAYS FROM ROCHE AND LC-MS/MS POST ACTH STIMULATION IN ADRENAL INSUFFICIENCY ASSESSMENT

Sema Okutan¹, Nanna Jørgensen¹, Stina Borresen¹, Lars Pedersen², Linda Hilsted³, Lennart Hansen⁴, Ulla Feldt-Rasmussen⁵, Marianne Klose¹

¹Copenhagen University Hospital, Rigshospitalet, Department of Endocrinology and Metabolism, Copenhagen, Denmark

²Næstved, Slagelse, and Ringsted Hospitals, Department of Clinical Biochemistry, Slagelse, Denmark

³Copenhagen University Hospital, Rigshospitalet, Department of Clinical Biochemistry, Copenhagen, Denmark

⁴Copenhagen University Hospital, Bispebjerg Hospital, Department of Clinical Biochemistry, Copenhagen, Denmark

⁵Copenhagen University Hospital, Rigshospitalet, Dept of Endocrinology, Pe 2132, Copenhagen, Denmark

Objective: Measurement of the concentration of cortisol is method dependent. Therefore, assay specific cut-offs for the definition of e.g., adrenal insufficiency should be available. The immunoassay Roche Elecsys Cortisol II (ElecsysCort II) is highly specific compared to Roche Elecsys Cortisol I (ElecsysCort I) which has been achieved using specific monoclonal antibody detection compared to earlier polyclonal counterparts.

The aim was 1) to establish assay specific cut-off values for the ACTH₁₋₂₄, Synacthen® test and 2) to investigate ElecsysCort II performance by comparison with the gold standard LC-MS/MS. In addition, to define local references of 6 other adrenocortical hormones.

Methods: One hundred healthy participants underwent a 250 µg Synacthen® test (50 men, age; 33 years (IQR 23-44), 50 women, age 40 years (IQR 33-55)). Blood samples were collected before, 30, and 60 min after Synacthen® injection. Plasma samples were analysed in triplicates with ElecsysCort I, ElecsysCort II, and LC-MS/MS. Also, 17-OH progesterone, corticosterone, cortisone, androstenedione, testosterone, and DHEAS, were measured with LC-MS/MS. Reference intervals were defined as the 2.5-97.5th percentiles, while the cut-off value for a normal cortisol response to the Synacthen® test was defined as the 2.5th percentile $-1.96 \times SE$.

Results: Cortisol concentrations were 21% (95% CI: 19-22%) lower when measured by ElecsysCort II as compared to ElecsysCort I. Cut-off levels for plasma cortisol 30 and 60 minutes after Synacthen® were 426 and 485 nmol/L by ElecsysCort II, respectively, and 411 and 470 nmol/L by LC-MS/MS, respectively. Reference intervals of the steroids were as follows: 17-OH progesterone: 1.3-8.1 nmol/L for men and 0.34-2.6 nmol/L for women ($P < 0.0001$); Corticosterone: 3.1-41 nmol/L for men and 3.5-54 nmol/L for women ($P = 0.43$); Cortisone: 44-84 nmol/L for men and 36-81 nmol/L for women ($P = 0.74$); Androstenedione: 1.6-4.8 nmol/L for men and 1.1-7.4 nmol/L for women ($P = 0.2$); Testosterone: 10-30 nmol/L for men and 0.33-1.6 nmol/L for women ($P < 0.0001$); DHEAS: 1.8-8.8 nmol/L for men and 0.40-8.2 nmol/L for women ($P = 0.0015$). The Synacthen® test resulted in significantly higher 30 min plasma 17-OH-progesterone, corticosterone, androstenedione, and DHEAS concentrations but lower cortisone concentrations in both sexes. Testosterone decreased in men ($P < 0.0001$) but increased in women ($P = 0.01$).

Conclusion: ElecsysCort II has a high analytical performance and measures significantly lower cortisol concentrations compared to previous polyclonal immunoassays. This difference is clinically relevant, and cut-offs must be changed to improve diagnostic precision. We recommend a 30 min cortisol cutoff of 411 nmol/L (LC-MS/MS) and 426 nmol/L (ElecsysCort II). As anticipated several adrenal steroid hormones increased upon ACTH-stimulation, except for cortisone and testosterone in men which decreased.

Abstract-ID: 178

EVALUATION OF EFFICACY AND SAFETY OF PASIREOTIDE IN PATIENTS WITH INADEQUATELY CONTROLLED ACROMEGALY.

Natalia Zawada¹, Jolanta Kunert-Radek¹

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

Introduction: Somatostatin analogues (SSA) remain the mainstay of pharmacological treatment for acromegaly. However, 40% of patients do not achieve disease control during therapy with first generation SSA. Data suggest that pasireotide, a novel multireceptor SSA, demonstrates superior efficacy over first generation SSA in the management of acromegaly.

Aim: Analysis of efficacy and safety of switching to pasireotide in patients with inadequately controlled acromegaly by first generation SSA.

Material&methods: Six patients with inadequately controlled acromegaly (GH>1ug/dl and IGF-1 upper limit normal) during long-term treatment with maximum doses of octreotide or lanreotide were enrolled in the study. They were switched to pasireotide 40mg every 4 weeks with the dose increase to 60mg/28 days when biochemical control of the disease was not achieved. When normalization of GH and IGF-1 had been observed for at least 12 weeks, pasireotide dose was decreased to 20mg every 4 weeks.

Results: Biochemical control of acromegaly was achieved in 5 patients. Moreover, pasireotide effectively and consistently reduced GH and IGF-1 levels in 3 patients just after 3 months of the therapy. Reduction of pasireotide dose to 20mg/28 days was no associated with deterioration of acromegaly control in these patients. Uncontrolled disease, which was observed in 2 patients, required the increase of pasireotide dose to 60mg every 4 weeks. Furthermore, patients with deterioration of glucose metabolism required modification of hypoglycemic agents with no need for cessation of pasireotide therapy. All patients had developed gall stones during therapy with first generation somatostatin analogues, however, 1 patient induced cholecystitis with indication for surgery when he was treated with pasireotide. This patient is still hospitalized due to intra-abdominal abscess after cholecystectomy.

Conclusion: Pasireotide is a promising therapeutic option for patients with not controlled acromegaly, however, it should be administrated in conjunction with strict glycemia control, particularly in diabetic patients. Moreover, long-term therapy with somatostatin analogues leads to cholelithiasis, therefore, cholecystectomy should be considered as soon as diagnosis of gall stones is confirmed.

Abstract-ID: 179

AVP DEFICIENCY IN A SEVERE CASE OF BEHÇET'S DISEASE

sara varela ribeiro¹, Marta Borges-Canha², ana varela³, joana queiros⁴

¹Endocrinology Department, Chsj, 319, Portugal

²Serviço de Endocrinologia, Diabetes e Metabolismo, Centro Hospitalar Universitário de São João, E.P.E, Porto, Portugal., Departamento de Cirurgia e Fisiologia, Faculdade de Medicina Da Universidade Do Porto., Department of Endocrinology, Diabetes and Metabolism, Porto, Portugal

³Chusj, Endocrinology, Diabetes and Metabolism, Portugal

⁴Chusj, Portugal

Introduction: Arginine Vasopressin Deficiency (AVP-D) is characterized by a high output of hypotonic urine and associated polydipsia due to impaired secretion of AVP. Reduced or absent AVP can result from disorders or lesions in the hypothalamus or pituitary. In rarer cases, AVP-D can develop in the context of systemic inflammatory diseases. Here we present an extremely rare case of AVP-D associated with Behçet's disease.

Case presentation: A 34-year-old woman was referred for an Endocrinology appointment due to complaints of polyuria and polydipsia. She had been diagnosed with Behçet's disease at the age of 20 after a longstanding history of recurrent oral aphthous ulcerations that began 10 years prior. Since diagnosis (oral aphthous ulcerations, optic neuritis and a positive pathergy test) and despite immunosuppressive therapy, she had developed erythema nodosum, renal disease (glomerulonephritis due to IgA nephropathy) and severe intestinal disease with multiple relapses, ultimately leading to a colectomy at the age of 30.

For the last four years the symptoms had been reasonably controlled with azathioprine (100+50 mg), except for a gradual exacerbation of polydipsia. Initially, she dismissed these complaints because she had always recalled drinking excessive amounts of water since she was a child as drinking would alleviate the discomfort caused by the ulcers. At the age of 16, Pediatrics had ruled out a diagnosis of AVP-D.

She had no history of past brain tumors, trauma, or infections of the central nervous system. A brain MRI showed multiple small T2 hyperintense lesions in various brain regions compatible with neuro-Behçet's, but without obvious pituitary involvement.

She was drinking >5L of water per day and would wake up an average of 2x each night due to thirst. Serum sodium was 138 mEq/L and serum osmolality 291 mOsm/kg. Urine output was 10,8l/24h and urine osmolality 57 mOsm/kg. A water deprivation test was performed, revealing an inability to concentrate urine with fluid restriction and a dramatic increase in urine osmolality after desmopressin administration. The patient was started on desmopressin 0.06 mg twice daily, resulting in a significant improvement in symptoms and quality of life.

Conclusion: Behçet's disease is a chronic inflammatory disorder of unknown cause. AVP-D is an extremely rare complication of Behçet's that may result from either vascular injury or neurohypophysitis. This case confirms Behçet's disease as a diagnosis to consider in AVP-D.

Abstract-ID: 181**PROLACTINOMAS IN MALES: CLINICAL RESPONSE TO MEDICAL THERAPY**

Inês Manique¹, Sara Amaral², Ana Palha¹, Luísa Cortez¹, Ahmets Sagarribay³, Luís Cerqueira⁴, José Silva-Nunes²

¹Centro Hospitalar Universitário Lisboa Central, Endocrinology, Diabetes and Metabolism, Lisboa, Portugal

²Centro Hospitalar Universitário Lisboa Central, Endocrinology, Diabetes e Metabolism, Lisboa, Portugal

³Centro Hospitalar Universitário Lisboa Central, Neurosurgery, Lisboa, Portugal

⁴Centro Hospitalar Universitário Lisboa Central, Neuroradiology, Lisboa, Portugal

Introduction: Prolactinoma in males are rare and usually more aggressive. However, majority of studies highlights the importance and effectiveness of dopamine agonists in this population.

Aims: Characterize male adult patients with prolactinomas and evaluate the response to dopamine agonists.

Methods: Retrospective study of the male patients of prolactinomas followed in a portuguese endocrinology department. Clinical, biochemical and imaging data, therapeutic approach and outcomes were assessed. We considered a significant imagiologic response if there was a > 50% reduction of the volume.

Results: A total of 46 patients were included with 45,8±16 years-old at diagnosis, 40 being macroadenomas with 25,5±10,1 mm. Parassellar, suprasellar and infrasellar growth was verified in 26, 25 and 18 patients respectively, and optic chiasm compression in 16. Initial prolactin level was 2480,7±3411,1 ng/mL (minimum 100 ng/mL and maximum 14650 ng/mL). Symptoms associated with hypersecretion (n=22) or mass effects (n=18) were the most common. Twenty seven patients presented hypopituitarism. Apoplexy was the first manifestation in 1 case. Eight patients had gynecomastia and 1 galactorrhea. Thirty six were treated medically (cabergoline – 25; bromocriptine – 11) with 34 normalizing prolactin under 6,1±2,8 mg/day of bromocriptine or 1,1±0,6 mg/week of cabergoline. The 2 patients without biochemical response were under >3 mg/week of cabergoline. A > 50% tumor reduction occurred in 26 patients (bromocriptine – 8; cabergoline – 18). The patients without imagiologic response (cabergoline – 7; bromocriptine – 3) were under 6,7 ± 3,8 mg/day of bromocriptine or 1,7 ± 0,9 mg/week of cabergoline (2 with ≥ 3 mg/week). Surgery was done in 10 patients, 5 because of apoplexy, 2 in the setting of spontaneous cerebrospinal fluid (CSF) fistulas and 3 were not observed by endocrinology before surgery. These patients maintained a residual tumoral and were treated medically, all of them normalizing prolactin but only 7 with imagiologic response. The patients without imagiologic response (bromocriptine – 1; cabergoline – 2) were under 7,5 mg of bromocriptine or 3 mg/week of cabergoline. We highlight that one of the patients was an atypical prolactinoma (Ki67 3-5%). Three patients under bromocriptine in the maximum tolerated dose without imagiologic response got a better response after changing to cabergoline.

Conclusion: This study suggests a clinical benefit of dopamine agonist namely in biochemical control of male patients with prolactinomas even after surgery. However, the absence of biochemical and/or imagiologic response under ≥ 3 mg/week dose of cabergoline or the maximum supported dose of bromocriptine suggests dopamine agonists resistance. This reinforces the fact that male sex is one of the risk factors for dopamine agonists resistance and may challenge the treatment.

Abstract-ID: 182

PARADOXICAL ACTH/CORTISOL RESPONSE TO MIXED MEAL TEST IN CUSHING'S DISEASE IS NOT CAUSED BY GIPR OVEREXPRESSION

Serena Avallone¹, Daniela Regazzo¹, Erica Santillo¹, Mattia Dalle Nogare², Luca Denaro³, Gianluca Occhi², Mattia Barbot⁴

¹Endocrinology Unit, Department of Medicine-Dimed, University Hospital of Padova, Padova, Italy

²Department of Biology, Padova, Italy

³Division of Neurosurgery - University Hospital of Padova, Padova, Italy

⁴Endocrinology Unit, Department of Medicine-Dimed, University Hospital of Padova, Department of Medicine-Dimed, Padova, Italy

Introduction: The abnormal expression of glucose-dependent insulinotropic polypeptide receptor (GIPR) has been recognized in various endocrine tumors. In particular, in GH-secreting pituitary adenomas (GH-PAs) and food-dependent adrenal Cushing's syndrome, GIPR illicit expression mediates the paradoxical increase respectively of GH and cortisol to the oral glucose tolerance test (OGTT). In medullary thyroid carcinomas, it is instead a marker for an advanced malignant process. Although GIPR overexpression has an incontrovertible role in these tumors, whether it may be involved in food-dependent hormone secretion has not been clearly established yet. Since we observed an unexpected ACTH and cortisol increase to the mix meal challenge (MMC) in a cohort of patients with ACTH-secreting pituitary adenomas (ACTH-PAs), we aimed to quantify the expression of steady-state GIPR RNA in a cohort of Cushing's disease (CD) patients and to correlate it with clinical features, attempting to establish whether the paradoxical ACTH/cortisol response identified in our patients could be caused by GIPR overexpression.

Methods: ACTH-PAs were removed by transsphenoidal resection in 54 CD patients (14 M/36 F; median age 39, IQR 30-48) diagnosed at our Endocrinology Unit. Three patients had a paradoxical ACTH and cortisol response to the MMC. RNA was extracted from tumoral tissues, and GIPR expression was evaluated by Droplet Digital PCR (ddPCR), which provides ultrasensitive detection and quantification of nucleic acid. ACTH-PAs GIPR expression was compared with GIPR-high GH-PAs taken as positive controls (Regazzo et al., 2017) and with normal pituitary as a negative control.

Results and Discussion: GIPR is not overexpressed in ACTH-PAs from patients, not even in those with a paradoxical ACTH/cortisol rise after MMC. In addition, GIPR RNA levels are not significantly different from those of normal pituitary. Thanks to ddPCR sensitivity we observed a slightly increased GIPR expression in an ACTH-PA with aggressive behavior, confirmed in a subsequent surgical removal. In conclusion, in the present cohort, GIPR expression levels are not involved in the paradoxical increase of ACTH and cortisol detected at MMC in some CD patients. Unlike in other endocrine tumors, GIPR does not appear to contribute to molecular pathogenesis in ACTH-PAs. Future steps will include the quantification of other receptors/targets affected by food intake, such as GLP-1 to better characterize the pathophysiological mechanisms of the ACTH/cortisol increase in CD.

Abstract-ID: 184

ACQUIRED IDIOPATHIC ISOLATED ADRENOCORTICOTROPIC HORMONE DEFICIENCY: A SYSTEMATIC REVIEW OF A HETEROGENEOUS AND UNDERREPORTED DISEASE.

Eugenie Van Mieghem¹, Christophe De Block², carlien de herdt³

¹*Antwerp University Hospital, Endocrinology, Edegem, Belgium*

²*Antwerp University Hospital, Department of Endocrinology, Antwerp University Hospital, Edegem, Belgium*

³*Antwerp University Hospital, Antwerp University Hospital, Department of Endocrinology-Diabetology-Metabolism, Antwerp, Belgium*

Background and aims: Acquired idiopathic isolated adrenocorticotrophic hormone deficiency (AIIAD) is a diagnosis of exclusion and a rare disease. Due to the nonspecific clinical presentation and ensuing underreporting, precise data on the prevalence are lacking. In this systematic review, we aimed to analyse the clinical characteristics, association with autoimmune diseases, and management of AIIAD. **Methods:** A structured search was conducted after developing a search strategy combining terms for AIIAD. Articles describing an adult case with diagnosis of ACTH deficiency using dynamic testing, no deficiency of other pituitary axes, and MRI of the brain/pituitary protocolled as normal, were included. Exclusion criteria were cases describing congenital isolated adrenal insufficiency (IAD), cases with a clear etiology for IAD, and articles where full text was not available.

Results: In total 42 articles were included, consisting of 85 cases. Distribution by sex was approximately equal (F:M; 47:38). Females were significantly younger (49.5 ± 17.1 years) at diagnosis compared to men (58.8 ± 18.2 years) ($p=0.017$). Lethargy was the most common presenting symptom (38%), followed by weight loss (25%), anorexia (22%), and myalgia/arthralgia (12%). Lethargy was significantly more frequent in females ($p=0.028$) while weight loss and anorexia were more common in men ($p=0.032$ and $p<0.001$, respectively). Eight cases (9.5%) presented with an Addison crisis. 31% of cases had an autoimmune disease at diagnosis of which Hashimoto hypothyroidism was the most frequent. No gender difference in autoimmunity was seen. Pituitary antibodies were screened in 26% of cases and were positive in 27%. Data about follow-up was scarce; dynamic testing was repeated in 4 cases of which 2 showed recovery of the adrenal axis.

Conclusion: We report the largest case series of AIIAD to date. An association between AIIAD and underlying autoimmune etiology was frequently noted. The value of the presence of anti-pituitary antibodies has yet to be investigated. In this review, we could not withhold AIIAD as a form of paraneoplastic syndrome as others have recently suggested because the 5 previous published case reports did not describe true AIIAD. Our systematic review highlights the lack of a clear definition and diagnostic work-up. We hypothesize the heterogeneity can be partly explained by not recognizing secondary causes of IAD, especially without MRI abnormalities such as glucocorticoid- and opioid-induced adrenal insufficiency. Based on the findings in this review a diagnostic flowchart is proposed. Follow-up data in literature are scarce, but we encourage considering to rechallenge the corticotropic and other pituitary axes.

Abstract-ID: 185

EFFICACY AND SAFETY OF PEGVISOMANT IN PATIENTS WITH ACROMEGALY – A REAL LIFE PERSPECTIVE FROM A TERTIARY CENTER

Helena Urbano Ferreira¹, Inês Meira², João Menino², Juliana Gonçalves³, Jorge Pinheiro⁴, Sandra Belo³, Jorge Pedro², Davide Carvalho⁵, Joana Queirós²

¹*Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo, Medicine Faculty of University of Porto, Centro Hospitalar Universitário São João, Serviço de Endocrinologia Diabetes e Metabolismo, Lisboa, Portugal*

²*Centro Hospitalar Universitário São João, Porto, Portugal, Department of Endocrinology, Diabetes and Metabolism, Portugal*

³*Centro Hospitalar Universitário São João, Porto, Portugal., Department of Endocrinology, Diabetes and Metabolism, Portugal*

⁴*Centro Hospitalar Universitário São João, Porto, Portugal., Department of Pathology, Portugal*

⁵*Faculty of Medicine, University of Porto, Porto, Portugal, Portugal*

Introduction: Pegvisomant is a growth hormone (GH) receptor antagonist used as second-line medical therapy in patients with acromegaly. Evidence suggests that pegvisomant is an effective and safe option, and it can be used in monotherapy or in combination with somatostatin analogs (SSAs).

Methods: Clinical files of patients with acromegaly treated with pegvisomant between 2003 and 2023 were reviewed. Data regarding clinical, biochemical and imagiological characteristics were collected. Biochemical control was defined as IGF-1 < 1.3xULN (upper limit of normal). Descriptive statistics were performed.

Results: Eleven patients were included, 72.7% female, mean age 44.3±10.0 years. All patients had previously undergone surgery, and, on histological examination, there were four (44.4%) somatotroph adenomas, four (44.4%) mammosomatotroph adenomas, and one (11.1%) plurihormonal adenoma. Two (18.1%) patients had previously undergone radiosurgery. All had previously been treated with first-generation SSAs, nine (81.8%) with an association of dopamine agonist and SSA, and three with pasireotide. Patients started pegvisomant due to inadequate disease control with previous regimens or due to drug intolerance/adverse effect. Ten patients started pegvisomant as monotherapy and one in addition to an SSA. Mean IGF-1 reduction was 47.1±28.6 ng/ml, and biochemical control was achieved in 9 (81.8%) patients. Among these, the maximum dose used was 70mg/week in four (44.4%) patients, and higher doses (105-140mg/week) were required in the remaining patients. During follow-up, three patients previously controlled with pegvisomant showed elevation of IGF-1 to levels >1.3ULN. SSA's were added in all, resulting in subsequent biochemical control in one patient. Two patients never achieved biochemical control with pegvisomant. The first one stopped pegvisomant four months after starting due to lipodystrophy at the injection site. The second one was resistant to 105mg/week of pegvisomant, and biochemical control was achieved after combining pegvisomant and SSA. Regarding adverse effects, in addition to one patient stopping therapy due to lipodystrophy, a second one reported altered sense of taste. Tumor growth was not observed in any patient during pegvisomant use (mean follow-up time 6.3±5.2 years).

Conclusion: Pegvisomant is an effective and safe drug in the treatment of acromegaly patients resistant to SSAs. In patients with more aggressive tumors resistant to pegvisomant, combination of pegvisomant and a SSA may further reduce IGF-1 and lead to adequate disease control.

Abstract-ID: 186

GIANT PROLACTINOMAS, A DETAILED ANALYSIS OF 196 ADULT CASES

carlien de herdt¹, Lisa Billion², Christophe De Block³

¹*Antwerp University Hospital, Antwerp University Hospital, Department of Endocrinology-Diabetology-Metabolism, Antwerp, Belgium*

²*Heilig Hart Ziekenhuis Lier, Endocrinology, Lier, Belgium*

³*Antwerp University Hospital, Department of Endocrinology, Antwerp University Hospital, Edegem, Belgium*

Purpose: Giant prolactinomas are a rare entity, representing approximately 5% of all prolactinomas. Previous articles revealed a male predominance, which was stated to be secondary to the diagnostic delay in men. A systematic review was performed and a comparison of the presentation, management and therapeutic outcomes in men versus women was made.

Methods: A structured search was conducted using the term 'giant prolactinoma' from 1981 until June 2022. Following inclusion criteria were used: ≥ 18 years, diameter ≥ 40 mm, prolactin levels > 1000 ng/ml and no concomitant GH/ ACTH secretion.

Results: 196 cases were included [age: 38 (28–50) years, F/M ratio: 1/3.6]. Maximum tumor diameter varied between 40-130 mm and was larger in men [54 mm (45–70)] compared to women [46 mm (42–62)]. Men had a numerically higher median prolactin level [9400 ng/ml (3845-22,831)] compared to women [8400 ng/ml (3002-15,000)]. The majority (91%) showed pituitary deficiency of which hypogonadotropic hypogonadism (88%) was the most frequent and similar between men and women. TSH, ACTH and GH deficiencies were seen in 55%, 42% and 38%, respectively, and were more frequently encountered in women compared to men. Most common presenting symptoms were visual impairment (73%) and headache (50%) in men and amenorrhea (58%) in women. 82% of cases were treated with a dopamine agonist (DA) as first-line treatment which led to normoprolactinemia, tumor shrinkage and visual improvement in 51%, 88% and 85% of cases, respectively. To achieve normoprolactinemia, a median dose of 2.0 (1.0-2.5) mg per week of cabergoline was prescribed. Surgery was performed in 29% of cases and all showed tumor remnant and persistent hyperprolactinemia. The main reasons to perform surgery as first-line treatment were visual impairment (43%) and suspicion of malignancy (43%).

Conclusion: Giant prolactinomas are rare and have a male predominance. Visual impairment is the most frequent presenting symptom in men and amenorrhea in women. The gender-related difference in tumor size and level of prolactin was confirmed in this analysis where men had a larger diameter and a higher baseline prolactin level. DAs are the treatment of choice, irrespective of tumor size and presence of visual impairment. As only half of the cases achieved normoprolactinemia we do not, in contrast to previous literature, state giant prolactinomas to be exquisitely sensitive to DAs. Patient characteristics associated with persistent hyperprolactinemia after treatment with a DA were female gender, higher baseline prolactin and larger tumor size. TSH- and ACTH-deficiency were more frequently encountered after surgery which was not seen for LH/FSH deficiency.

Abstract-ID: 193

MOLECULAR AND CLINICAL ASPECTS OF PROLACTINOMAS

Mijgona Safarova¹, Zamira Khalimova²

¹*Republican Center of Endocrinology*

²*Republican Specialized Scientific-Practical Medical Center of Endocrinology, Republican Center of Endocrinology, Republican Center of Endocrinology, Tashkent, Uzbekistan*

Aim: To study the molecular and clinical characteristics of PRL-secreting pituitary adenomas and to develop new approaches to therapy.

Materials and research methods: The object of the study were patients with prolactinomas in the national data registry of the Republic of Uzbekistan, consisting of 321 patients at the Republican Specialized Scientific and Practical Center of Endocrinology named after Academician Y.Kh. Turakulov. The age of the subjects ranged from 11 to 72 years, the average age was -44.2 ± 3.5 , of which 172 (53.6%) patients were female and 149 (46.4%) men. All 321 patients underwent studies of somatic, endocrine, hormonal status: prolactin, LH, FSH, TSH, free T4, progesterone, estradiol, testosterone (by the ICL method), neuroimaging and neuro-ophthalmological assessment in the form of MRI/CT of the chiasmatic-sellar region, consultation with an ophthalmologist, genetic studies - PCR (real-time), determination of the molecular weight of prolactin (using the method of enzymatic enhanced chemiluminescence on the Immulite 2000 XPI device).

Results: Patients are divided into 4 groups:

Group I consisted of 100 patients with microprolactinomas (tumor size up to 10 mm). Of these, 89 (27.7%) were women and 11 (3.4%) were men, respectively.

Group II consisted of 93 patients with macroprolactinomas (tumor size more than 10 mm). Of these, 34 (10,6%) were women and 59(18,3%) men.

Group III consisted of 68 patients with resistant prolactinomas, of which 30(9,3%) were women and 38 (11,8%) men, respectively.

Group IV consisted of 60 patients with an aggressive course of prolactinoma: 19 (5,9%) women and 41 men (12,7%), respectively, based on the degree of aggressiveness and invasion of adenoma, group IV was divided as follows: subgroup IV (A) is invasion of degrees 1 and 2, 7 (36,8%) women and 19 (46,3%) men and IV (B) subgroup invasion of degrees 3 and 4, 12 (63,2%) women and 22 (53,7%) men, respectively.

Conclusions: The algorithm for prolactin therapy has been improved, where the main characteristic of traditional therapy is aimed at identifying early predictors of aggressive and resistant prolactinomas. Determination of molecular weight can become a predictor of early diagnosis and determine further tactics for the management and treatment of patients with prolactinomas.

Abstract-ID: 194

TWO RARE CASES OF CENTRAL DIABETES INSIPIDUS

Marina Koulenti¹, Aristidis Diamantopoulos¹, Eirini Partsalaki¹, Panagiotis Mouchtouris¹, Konstantinos Petsanis¹, Georgia Ntali¹, Marinella Tzanela¹

¹*Evangelismos General Hospital, Endocrinology, Diabetes and Metabolism, Athens, Greece*

Central Diabetes Insipidus (CDI) is a rare disorder characterized by the deficiency of arginine-vasopressin secretion. It typically presents with dilute polyuria, nocturia and most of the times polydipsia and plasma hyperosmolality. Common causes are tumors of Central Nervous System, infiltrative disease, autoimmunity, trauma, or idiopathic. Hereby, we present two rare cases of CDI admitted to our hospital.

1st case): A 62 years old female presented to the emergency department due to gradual upper limb weakness. CT chest revealed a left lung mass of the upper lobe, while a cervical MRI showed a spine mass, pituitary stalk thickening and heterogenous enhancement of pituitary gland. The patient was admitted to Neurosurgical department and dexamethasone treatment was initiated. Upon investigation, she revealed that she reported polyuria and polydipsia during the previous four weeks. She was haemodynamically stable, her plasma sodium was 142 mmol/L, potassium was 4.6 mmol/L and the urine specific weight was 1006. Urine output after 8h was 4lt, so desmopressin was started. FT4 was normal 1,4 (0.8-1.8). Histopathology of the cervical mass showed a lung adenocarcinoma metastasis. She was later transferred to the oncology department to continue her treatment.

2nd case): An 84 years old male with a history of IgG4 nephropathy, for which he was on 5 mg methylprednisolone daily, was admitted at the Cardiology department to undergo a coronary angiography. He reported polyuria and polydipsia, while diabetes mellitus was absent. MRI revealed a pituitary stalk thickening and subsequently IgG4 hypophysitis was suspected. Desmopressin was started along with an increase of methylprednisolone dose to 32 mg per day and gradual tapering during the following months. At last follow up of the patient, six months after his admission, diabetes insipidus has completely resolved.

Conclusions: The presentation and the course of patients with CDI can vary greatly, depending on the cause. CDI is the clinical manifestation of a number of underlying diseases, and further investigations are needed to clarify the underlying diagnosis.

Abstract-ID: 196

EARLY CLINICAL AND DIAGNOSTIC CRITERIA FOR THE DETECTION OF AGGRESSIVE PITUITARY ADENOMAS

Ozoda Azimova¹, Zamira Khalimova²

¹Republican Specialized Scientific and Practical Medical Center of Endocrinology Named after Academician Yo. Kh. Turakulov., Neuroendocrinology, Tashkent, Uzbekistan

²Republican Specialized Scientific and Practical Medical Center of Endocrinology Named after Academician Yo. Kh. Turakulov, 2Republican Specialized Scientific Practical Medical Center of Endocrinology of Public Health Ministry Named by Acad. Ya.Kh. Turakulov-., Neuroendocrinology, Tashkent, Uzbekistan

Despite the fact that most pituitary adenomas are benign in nature, do not have the ability to invasiveness and aggressive flow metastasize, however from 25 up to 55% are invasive and aggressive. The purpose of this work was to study the early clinical and diagnostic characteristics of aggressive pituitary adenomas depending on gender and age peculiarity. The subject of the study was 100 patients with a confirmed diagnosis of pituitary adenoma with invasive growth 1-2 stage by Knops classification (IIA group) and invasion 3-4 stage (IIB group) .

Clinical analysis showed that with paracellular growth (30%) of adenomas, the main complaints of patients from 77% to 97% were associated with the syndrome of damage to the cavernous sinus, which are characterized by the involvement of the III, IV and VI craniocerebral nerves such as ptosis, strabismus, trigeminal pain, due to damage to r.opthalmicusn.trigemini and violation cerebrovascular accident. With infracellular growth, the main complaint of liquorarea (17%). With suprasellar growth of invasive adenomas in patients with IIA and IIB groups, the frequency of complaints regarding visual decline was 50% (n = 13) and 43.6% (n = 17), respectively, and a narrowing of visual fields was also found 26.9% (n = 7) and 66.7% (n = 26), respectively, to a significant extent (p < 0.001) higher compared to non-invasive adenomas. Also, statistically significant complaints (p < 0.001), but to a relatively lesser extent there were complaints such as hypoacusia 53% (n = 21) and ataxia 69.2% (n = 27), which were recorded to the greatest extent in grade 3-4 invasions (IIB group).

Clinical analysis showed that with parasellar growth (30%) of adenomas, the main complaints of patients from 77% to 97% were associated with the syndrome of involvement of the cavernous sinus. It was found that clinical assessment of adenoma volume and hormonal diagnosis cannot predict the aggressive course of adenomas. So, structural changes in adenoma (heterogeneity), intensive growth (> 20% over 6 months) of adenoma over time, hyperintensities in T2 mode contribute to a more thorough study of patients with AH and the determination of markers for the diagnosis of aggressiveness.

Abstract-ID: 203

INVESTIGATING MRI T2-SIGNAL INTENSITY- DERIVED PARAMETERS AND THEIR ROLE IN PREDICTING THE SOMATOSTATIN ANALOGUE RESPONSE IN SOMATOTROPH PITNETS- COMPARISON OF QUANTITATIVE AND QUALITATIVE APPROACH.

Magdalena Godlewska¹, Anna Grochowska², Anna Bogusławska³, Alicja Hubalewska-Dydejczyk⁴, Aleksandra Gilis-Januszewska¹

¹Jagiellonian University Medical College, Chair and Department of Endocrinology, Jagiellonian University, Medical College, Cracow, Poland, Department of Endocrinology, Cracow, Poland

²Jagiellonian University Medical College, Department of Radiology, Cracow, Poland

³University Hospital in Kraków, Jagiellonia University Medical College, University Hospital in Kraków, Kraków, Poland

⁴Jagiellonian University, Department of Endocrinology, Chair of Endocrinology, Krakow, Poland

Introduction and purpose

T2-signal intensity (SI) of the somatotroph Pituitary Neuroendocrine Tumor (sPitNET) has been associated with histopathological characteristics and treatment response. Various approaches to its assessment are proposed but no unification has been reached so far. We aimed to compare qualitative and quantitative methods of SI assessment and investigate quantitative T2-derived radiological parameters and their possible clinical implications.

Methods

This single-center study involved 69 out of 117 consecutive patients newly-diagnosed with acromegaly. Tumors were divided into 3 groups using qualitative and quantitative assessment methods in T2-weighted MRI images: hyperintensive (HYPER), isointensive (ISO) and hypointensive (HYPO). Qualitative method was based on visual comparison between intensity of sPitNET vs. grey matter. Quantitative assessment involved measurement of SI of sPitNET, grey and white matter. Firstly, the division into intensity groups was based on calculated Signal Intensity Ratio of PitNET's vs. gray matter's intensity (GM-SIR). For HYPO SIR was <0.8 , for ISO between 0.8 and 1.2, and >1.2 for HYPER. Secondly, measurements of SI of sPitNETs were compared to SI measurements of grey and white matter. sPitNET's intensity higher than grey matter classified as HYPER, lower than white matter's SI classified the tumor as HYPO, while values between grey and white matter's quantified SI were classified as ISO.

Finally, we investigated two T2-derived signal intensity parameters: GM-SIR and PitNET's vs. White Matter Signal Intensity Ratio (WM-SIR). ROC curves cut-off points predicting response to somatostatin analogues (SSA) for GM-SIR and WM-SIR were calculated.

Results

Quantitative and qualitative methods classified correspondingly in 65% of cases. According to all methods HYPER and ISO tumors were larger than HYPO, HYPO were more biochemically active per unit of the tumor volume. GM-SIR did not predict the treatment response to preoperative somatostatin analogues (SSA). Univariate logistic regression showed that WM-SIR predicted the biochemical control after SSA. Using the ROC curve, the optimal cut-off point of WM-SIR predicting the response to SSA was 1.1363, with Area under the curve of 0.686 (95% CI 0.524-0.848, $p=0.024$). Using this criterion, patients with higher WM- SIR had larger tumors but less biochemically active per tumor volume unit.

Conclusion

Our study demonstrated the discrepancies between the results obtained using qualitative and quantitative methods. WM- SIR predicted the outcome of pharmacological treatment. Further, multi-center studies are required to unify the SI assessment and prove its applicability in the everyday management of acromegaly.

Abstract-ID: 204

SYSTEMATIC REVIEW AND META-ANALYSIS OF USP8 MUTATIONS IN 1777 CORTICOTROPH TUMOURS

Prajina Sharma¹, Vivian von Selzam², Martin Reincke³, Marily Theodoropoulou⁴, Luis Gustavo Perez-Rivas⁵

¹Department of Medicine IV, University Hospital, LMU Munich, Munich, Germany

²Department of Medicine IV, University Hospital, LMU Munich, München, Germany

³Ludwig-Maximilians-University, Medizinische Klinik IV, Endocrine Research Unit, München, Germany

⁴Ludwig-Maximilians-Universität München, Mediv, München, Germany

⁵Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, LMU München, München, Germany

Background: Somatic *USP8* mutations are common in corticotroph tumours, but their reported prevalence and association with clinical features is very variable among studies.

Aim of the study: Determine prevalence and clinical relevance of *USP8* mutations.

Methods: Systematic review and meta-analysis of existing literature. We used Pubmed, Embase, Scopus and Web of Science databases. Selected terms: pituitary gland (Mesh), pituitary ACTH Hypersecretion (MeSH), ACTH-Secreting Pituitary Adenoma (Mesh), Cushing disease (Mesh), PitNET, *USP8*, mutation, variant, genetics. Inclusion criteria: original studies including ≥ 3 human patients with CD reporting *USP8* mutational status. Exclusion criteria: no human research, lack of *USP8* mutational information, lack of clinical data (< 3 patients). Data was evaluated by 3 independent authors. A random effects model meta-analysis and meta-regression were performed.

Results: From 3009 extracted records, we preselected 281 full-text assessed for eligibility and kept 37 publications for a meta-analysis. In total, we included 1777 patients (median number of patients/publication 37, range 5-217). Corticotroph tumours with *USP8* mutations were reported in 610 out of 1777 (34.3%) patients, with a mean prevalence among studies of 33.5% (32.7-34.3 95% CI, range 0-77%) and median of 31.0% (IQR 22.7-41.9%). Patients with *USP8* mutant tumours were mostly female (OR 3.90 to wild type, 95%CI 2.76-5.51, 95%PI 2.72-5.6; $P < 0.001$; $n = 30$ publications), with higher BMI (mean difference 1.53 kg/m², 95%CI 0.34-2.72 kg/m²; 95%PI -0.23-3.29 kg/m²; $P = 0.012$; $n = 7$), and in average 5 years younger at diagnosis (95%CI 2-8 years, 95%PI 6-16 years; $P < 0.001$; $n = 23$). Postoperative remission was more frequently achieved in patients with *USP8* mutant tumours (OR 1.75, 95%CI 1.15-2.64, 95%PI 0.8-3.81; $P = 0.008$; $n = 18$). However, they were more likely to recur than patients with wild type tumours (OR 2.08, 95%CI 1.02-4.27, 95%PI 0.36-11.97; $P = 0.045$; $n = 10$). We did not find significant differences regarding other clinical or tumour variables, mostly due to heterogeneity among studies. A meta-regression showed that variability of *USP8* mutation prevalence among studies was related to female/male ratio (adjusted $R^2 = 0.198$; $P = 0.029$) but not to tumour size or invasion.

Conclusion: the present meta-analysis shows that patients with *USP8* mutant tumours are mostly female, with higher BMI and more likely achieve postoperative remission, but are at higher risk of recurrence than those with wild type tumours.

Abstract-ID: 211

SECOND-LINE MEDICAL THERAPY IN ACROMEGALY – EXPERIENCE WITH PEGVISOMANT

Ana Torrão Pinheiro¹, Andreia Martins Fernandes², Maria Teresa Pereira¹, Isabel Ribeiro³, Cláudia Amaral⁴

¹*Centro Hospitalar Universitário de Santo António, Endocrinology Department, Porto, Portugal*

²*Instituto Português de Oncologia de Coimbra Fg, Endocrinology Department, Coimbra, Portugal*

³*Centro Hospitalar Universitário de Santo António, Neurosurgery Department, Porto, Portugal*

⁴*Chuporto, Centro Hospitalar Universitário de Santo António, Chuporto, Oporto, Portugal*

Introduction: Acromegaly is associated with increased mortality, especially in cases of persistent active disease. Surgical resection of a pituitary adenoma is the first-line treatment in the majority of patients, and medical treatment with first-generation somatostatin analogs (1st-gen SSA) is indicated if the disease persists. Several studies report that biochemical control was not achieved in 24-65% of patients treated with 1st-gen SSA. Second-line medical therapy includes second-generation SSA - Pasireotide - and growth hormone receptor antagonist - Pegvisomant. They are indicated in patients without cure after surgery and without biochemical control with 1st-gen SSA. However, the treatment should be personalized and take into account clinical, molecular, and morphological characteristics of each patient and tumor.

Clinical Cases: We present a case series of 3 patients with acromegaly that constitutes our experience with Pegvisomant. Here we aim to review the reasons that lead to introduction of Pegvisomant and other possible choices of therapy for each case. We were unable to conduct an immunohistochemistry study to evaluate somatostatin receptor subtypes due to unavailability at our center. The age of diagnosis ranged from 32 to 38 years (median 34,6 years); 2 men and 1 woman were included; and all had a macroadenoma. At diagnosis, IGF-1 levels ranged from 750-1466ng/mL, 2 patients had hypertension and 1 had Diabetes Mellitus. All patients were submitted to transsphenoidal surgery without cure, and started treatment with 1st-gen SSA within 2 months after surgery. All patients were submitted to radiotherapy in the course of disease since they were not controlled with medical therapy. Case 1 started pegvisomant 10mg daily after partial response to lanreotide 120mg every 4 weeks and cabergoline 1,5mg weekly. IGF-1 levels are now controlled with pegvisomant 15mg daily after 36 months postoperative. Case 2 started pegvisomant 10mg daily after partial response to pasireotide LAR in a clinical trial and worsening of glycemc control that led to its discontinuation. At last follow up, IGF-1 was 1.7x upper limit of normal (ULN) with pegvisomant 20mg daily and cabergoline 2mg weekly at 105 months postoperative. Case 3 started pegvisomant 10mg daily after partial response to lanreotide 120mg every 4 weeks and bromocriptine 10mg daily. IGF-1 levels are now 1.33xULN with pegvisomant 20mg daily at 63 months postoperative.

Discussion: The approach to a patient with treatment-resistant acromegaly is challenging, requiring a multidisciplinary evaluation, and consideration of several characteristics: achievement of biochemical control (levels of IGF-1 and GH); tumor size and invasion; symptoms and comorbidities; and cost-effectiveness evaluation of each therapy and availability at each center.

Abstract-ID: 212

A RARE ASSOCIATION OF PROLACTINOMA AND CUSHING'S DISEASE IN THE SAME PATIENT WITH DOUBLE ASYNCHRONOUS PITUITARY LESIONS – A CASE REPORT

Tiberiu Manole¹, Ionela Baciu¹, Anda Dumitrascu², Ionut Gobej³, Catalina Poiana¹

¹*C I Parhon National Institute of Endocrinology, Pituitary and Neuroendocrine Pathologies, Bucharest, Romania*

²*C I Parhon National Institute of Endocrinology, Radiology, Bucharest, Romania*

³*Neurohope Neurosurgery Clinic, Neurosurgery, Bucharest, Romania*

Background: Microprolactinomas are the most frequent functional pituitary tumours and in most cases medical treatment is the first line of therapy, controlling both tumour growth and prolactin levels. Cushing's disease is one of the rarest functional pituitary tumours, caused by an ACTH-producing pituitary adenoma having a clear surgical indication, with limited response to medical treatment which has serious adverse reactions. The clinical finding of the 2 distinct diseases in the same patient with 2 adenomas is a very rare occurrence and almost always they are synchronous.

Objectives and Methods: To present a retrospective observational case report of a 62-years-old female with a long evolution of a microprolactinoma, who developed a secondary ACTH-producing pituitary adenoma.

Results: The patient was amenorrhic from the age of 39 and in 2009 (48 years old) was diagnosed with a right pituitary microprolactinoma, the rest of the anterior pituitary function was preserved - dopamine agonist treatment was initiated. Over the years she developed type 2 diabetes mellitus, arterial hypertension and osteopenia and in 2016 the bloodwork showed high basal ACTH with optimal cortisol suppression on 2x2 dexamethasone test (results stable on several follow-ups), while the pituitary CT showed stable size of the microprolactinoma. In 2019 she presented with a Cushing phenotype, a new left pituitary adenoma was identified, high ACTH and midnight salivary cortisol and unsuppressed serum cortisol on the 2x2 test, diagnosing Cushing's disease. Petrosus sinus sampling would have certified the etiological diagnosis - unavailable in Romania.

She underwent double adenoma excisions with partial transient secondary adrenal insufficiency, the rest of the pituitary function was preserved – a low dose glucocorticoid substitution was started. Also, the metabolic complications greatly improved after surgery – probably the diabetes mellitus and hypertension were secondary to the Cushing's and were the first signs of the disease. Seven months post-surgery, a new left pituitary lesion was discovered, ACTH was in the high normal limit, with a normal basal cortisol level and optimal cortisol suppression – substitution was stopped. Two years after surgery - high ACTH with a suboptimal cortisol suppression test, while the pituitary MRI revealed a stable size for the new adenoma. UFC could not be collected because of the patient's urinary incontinence. The metabolic complications were stable and her prolactin level was normal – reevaluation in 6 months is needed.

Conclusions: Asynchronous double pituitary lesion with microprolactinoma and Cushing's disease is a very rare and unexpected finding, therefore close surveillance of the global pituitary function and imaging are mandatory at follow-ups, as well as the screening for the systemic complications of the Cushing's.

Abstract-ID: 214

PITFALLS IN DIAGNOSIS OF THE PITUITARY STALK LESION: INFUNDIBULO-NEUROHYPOPHYSITIS OR GERM CELL TUMOR?

Salvatore Raia¹, Antonio Bianchi¹, Antonella Giampietro¹, Tommaso Tartaglione², Carmelo Caldarella³, Mario Rigante⁴, Marco Gessi⁵, Liverana Lauretti⁶, Pierpaolo Mattogno⁶, Laura De Marinis⁷, Alessandro Olivi⁸, Alfredo Pontecorvi⁷, Francesco Doglietto⁸, Sabrina Chiloiro⁷

¹Fondazione Policlinico Universitario A. Gemelli Irccs, Rome, Italy, Università Cattolica del Sacro Cuore, Rome, Italy, Pituitary Unit; Internal Medicine, Endocrinology and Diabetes Unit; Department of Medical and Surgical Sciences, Rome, Italy

²Fondazione Policlinico Universitario A. Gemelli Irccs, Rome, Italy, Università Cattolica del Sacro Cuore, Rome, Italy, Radiology and Neuroradiology Unit; Department of Imaging, Radiation Therapy and Hematology, Rome, Italy

³Fondazione Policlinico Universitario A. Gemelli Irccs, Rome, Italy, Università Cattolica del Sacro Cuore, Rome, Italy, Nuclear Medicine Unit; Department of Imaging, Radiation Therapy and Hematology, Rome, Italy

⁴Fondazione Policlinico Universitario A. Gemelli Irccs, Rome, Italy, Università Cattolica del Sacro Cuore, Rome, Italy, Otorhinolaryngology, Head and Neck Surgery; Department of Aging, Neurological, Orthopedic and Head-Neck Sciences, Rome, Italy

⁵Fondazione Policlinico Universitario A. Gemelli Irccs, Rome, Italy, Università Cattolica del Sacro Cuore, Rome, Italy, Neuropathology Unit; Pathology Unit of Head and Neck, Lung and Endocrine Systems, Rome, Italy

⁶Fondazione Policlinico Universitario A. Gemelli Irccs, Rome, Italy, Università Cattolica del Sacro Cuore, Rome, Italy, Neurosurgery Unit; Department of Neurosciences, Rome, Italy

⁷Fondazione Policlinico Universitario A. Gemelli Irccs, Rome, Italy, Pituitary Unit; Internal Medicine, Endocrinology and Diabetes Unit; Department of Medical and Surgical Sciences, Italy

⁸Fondazione Policlinico Universitario A. Gemelli Irccs, Rome, Italy, Neurosurgery Unit; Department of Neurosciences, Italy

Introduction: Infundibulo-neurohypophysitis (INH) is an uncommon inflammatory disorder. Because of the location of inflammation, it selectively affects the neuropituitary and pituitary stalk. The differential diagnosis remains challenging with neoplastic lesions, such as germ cell neoplasia, Langerhans cell histiocytosis, Erdheim-Chester Disease, metastasis. Our clinical case is emblematic for pitfalls in diagnosis of the pituitary stalk lesion.

Case report: A 18 years-old male patient was observed at our Center Pituitary in July 2023, for pan-hypopituitarism due to a pituitary stalk lesion. The patient was also affected from Klinefelter syndrome. The patient medical history had started when he was 10 years-old with polyuria/polydipsia. On May 2021, the patient was admitted to the Endocrinology department of another hospital, for asthenia, pubertal delay and persistence of polydipsia/polyuria. Pituitary hormone tests documented pan-hypopituitarism and diabetes insipidus. Hormonal replacement therapy with hydrocortisone, levothyroxine and desmopressin acetate was prescribed. Campimetry evaluation proved a bilateral hemianopsia. A pituitary and brain contrasted MRI proved a sellar and suprasellar lesion, suggestive for a germinoma. Pituitary biopsy was performed, resulting undiagnosed. Therefore, on June 2021, a second pituitary biopsy was conducted, with detection of few cells, mainly immune ones (B CD20+ and T CD3+), histiocytes and negative immunohistochemistry for c-Kit, PLAP, CD1a, SI 00, MPO, CD30, CD15. The patient was diagnosed for INH. On April 2022, the patient referred to another endocrinology department for a second opinion, where G4 immunoglobulins were dosed resulting normal, antinuclear antibodies were positive, and pituitary MRI showed unchanged the pituitary stalk lesion, and the empty sella due to previous pituitary biopsies. An 18- fluorodeoxyglucose (18-FDG) positron emission tomography computed tomography (PET-CT) showed a suprasellar tracer hyperaccumulation (SUV 23.2). Patient was treated with high dose corticosteroid therapy (methylprednisolone 1 gr for 3 days), without a clinical and neuroradiology improvement. On October 2022, a pituitary MRI showed a reduction in size of the tissue sited in the suprasellar space, in absence of resolution of the campimetry deficit. The patient was referred to our Pituitary centre for an additional neurosurgical evaluation, for ruling out alternative diagnosis and considering a third neurosurgical debulking. An endocrine evaluation confirmed the pan-hypopituitarism, the pituitary MRI showed unchanged the pituitary stalk lesion but a neuroradiological evaluation together with 18F-Fluorocholine PET-CT was suggestive for a germ cell tumor. A third surgery is now scheduled.

Conclusion: Our clinical case confirms the difficult in the differential diagnosis of pituitary stalk lesions, underlining the need of a multidisciplinary approach also considering the emerging role of functional imaging.

Abstract-ID: 215

THE GENETIC BACKGROUND OF ACROMEGALY IN A TERTIARY REFERRAL CENTRE IN KRAKOW, POLAND

Anna Bogustawska¹, Magdalena Godlewska², Aleksandra Gilis-Januszewska³, Márta Korbonits⁴, Alicja Hubalewska-Dydejczyk⁵, Aleksandra Gilis-Januszewska²

¹University Hospital in Kraków, Jagiellonia University Medical College, University Hospital in Kraków, Kraków, Poland

²Jagiellonian University Medical College, Chair and Department of Endocrinology, Jagiellonian University, Medical College, Cracow, Poland, Department of Endocrinology, Cracow, Poland

³Department of Endocrinology, Jagiellonian University, Chair and Department of Endocrinology, Jagiellonian University, Medical College, Cracow, Poland, Cracow, Poland

⁴Barts and The London School of Medic, Queen Mary University of London, BA and the London School of Medicine, London, United Kingdom

⁵Jagiellonian University, Department of Endocrinology, Chair of Endocrinology, Krakow, Poland

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 134 patients (79 females, 55 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 12.7% (17/131) patients presented clinical manifestations of syndromic disease or gene variants which might be associated with acromegaly.

AIP variants were identified in 7.7% (8/105), *MEN1* alterations were detected in 3.6% (4/84), 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: Genetic testing in acromegaly should be considered to personalize and optimize the assessment and treatment of patients and to benefit their family members.

Abstract-ID: 218

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.

Ewelina Rzepka¹, Joanna Kokoszka², Marta Opalińska³, Katarzyna Sitarz⁴, Anna Grochowska⁵, Anna Sowa-Staszczak³, Alicja Hubalewska-Dydejczyk³, Aleksandra Gilis-Januszevska³

¹Jagiellonian University Medical College, Chair and Department of Endocrinology, Krakow, Poland, Warsaw, Poland

²Endocrinology, Oncologic Endocrinology and Nuclear Medicine Department, University Hospital in Krakow, Poland, Poland

³Jagiellonian University Medical College, Chair and Department of Endocrinology, Krakow, Poland, Poland

⁴University Hospital in Krakow, Poland, Poland

⁵Department of Radiology, University Hospital in Krakow, Poland, Poland

Introduction

2-[18F]FDG PET/CT, commonly used for neoplastic lesions detection, also allows assessment of the severity of the inflammatory process in muscles. Patients with Cushing syndrome (CS) demonstrate many metabolic changes including worsening of muscle quality. Some mechanisms, involving muscle steatosis, myopathy, are known, but their relationship to glucose metabolism is not well investigated. Ectopic adrenocorticotropin secretion (EAS) accounts for 10-15% of cases of CS.

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.

Materials and Methods

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) were 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 in both right and left muscle groups and target to background ratio (TBR) 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.

Results

The comparison of glucose metabolism muscle and fat composition assessed by 2-[18F]FDG-PET and CT respectively, showed inverse correlation between ACTH concentration and SUV mean ($p=0.04$) and SUV peak ($p=0.03$) of psoas muscle. Moreover, survival time was positively correlated with SUV mean of psoas muscle ($p=0.04$), TBR of psoas ($p=0.003$) and femoris muscle ($p=0.03$).

Conclusions

Increased SUV mean of psoas muscle and TBR of psoas and femoris muscles were associated with longer survival. It may reflect better general condition of the patients with better muscle quality. 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.

Abstract-ID: 220

EXCESS MORTALITY IN PATIENTS WITH NON-FUNCTIONING PITUITARY ADENOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Fabio Bioletto¹, Michela Sibilla², Daniela Cuboni², Luigi Aversa², Emanuele Varaldo², Alessandro Berton², Nunzia Prencipe², Valentina Gasco², Ezio Ghigo², Silvia Grottoli³

¹*Division of Endocrinology, Diabetes and Metabolism; Department of Medical Sciences; University of Turin; Turin, Italy,*
²*Division of Endocrinology, Diabetes and Metabolism; Department of Medical Sciences, Turin, Italy*

²*Division of Endocrinology, Diabetes and Metabolism; Department of Medical Sciences; University of Turin; Turin, Italy, Italy*

³*Division of Endocrinology, Diabetes and Metabolism, Division of Endocrinology, Diabetes and Metabolism; Department of Medical Sciences; University of Turin; Turin, Italy, Turin, Italy*

Background. Patients with non-functioning pituitary adenoma (NFPA) often present with a variety of clinical manifestations and comorbidities, mainly determined by the local mass effect of the tumor and by hypopituitarism. Whether this has an impact on overall mortality, however, is still unclear.

Objective. The aim of this systematic review and meta-analysis was to address the all-cause mortality risk in patients with NFPA.

Methods. PubMed/Medline, EMBASE, and Cochrane Library databases were systematically searched until May 2023 for studies reporting data about standardized mortality ratios (SMRs) in patients with NFPA. Effect sizes were pooled through a random-effect model. This systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO, #CRD42023417782).

Results. A total of 622 records were identified in the initial literature search. Removal of duplicates led to an overall pool of 469 studies. An accurate title and abstract revision was sufficient to exclude 445 articles as not pertinent or not fulfilling our prespecified inclusion or exclusion criteria; the remaining 24 studies were assessed in full text for eligibility. In the end, 5 studies evaluating SMR in patients with NFPA fulfilled all eligibility criteria, encompassing 23,123 subjects with a total follow-up time of approximately 130,000 person-years; one further study reported data stratified by sex relative to the cohort of patients of one of the previous five. Patients with NFPA showed an increased mortality risk compared to the general population (SMR=1.57 [95%CI: 1.20-1.99], $p<0.01$). Age and sex appeared to act as effect modifiers, with a trend towards higher SMRs in females (SMR=1.57 [95%CI: 0.91-2.41], $p=0.10$) than in males (SMR=1.00 [95%CI: 0.89-1.11], $p=0.97$), and in patients diagnosed at age 40 years or younger (SMR=3.19 [95%CI: 2.50-3.97], $p<0.01$) compared to those with later onset of the disease (SMR=1.26 [95%CI: 0.93-1.65], $p=0.13$). The trend towards excess mortality was similar in patients with normal (SMR=1.22 [95%CI: 0.94-1.53], $p=0.13$) or deficient (SMR=1.26 [95%CI: 0.82-1.79], $p=0.27$) pituitary function.

Conclusions. Excess mortality is observed in patients with NFPA, regardless of pituitary function, especially in women and in patients with a younger age at diagnosis.

Abstract-ID: 221

MID-PARENTAL HEIGHT IMPROVES THE DIAGNOSIS OF TALL STATURE AND GIGANTISM IN ADULT PATIENTS WITH ACROMEGALY

Anna Bogustawska¹, Magdalena Godlewska², Márta Korbonits³, Jerzy Starzyk⁴, Alicja Hubalewska-Dydejczyk⁵, Aleksandra Gilis-Januszewska²

¹University Hospital in Kraków, Jagiellonia University Medical College, University Hospital in Kraków, Kraków, Poland

²Jagiellonian University Medical College, Chair and Department of Endocrinology, Jagiellonian University, Medical College, Cracow, Poland, Department of Endocrinology, Cracow, Poland

³Barts and The London School of Medic, Queen Mary University of London, BA and the London School of Medicine, London, United Kingdom

⁴3. Department of Paediatric and Adolescence Endocrinology, Paediatric Institute, Jagiellonian University Medical College, Krakow, Poland

⁵Jagiellonian University, Department of Endocrinology, Chair of Endocrinology, Krakow, Poland

Objectives: Tall stature (TS) in acromegaly patients could be a manifestation of growth hormone (GH) excess before epiphysis closure. The aim of this study was to evaluate the relationship between the height of patients with GH excess related to mid-parental height (MPH) and population mean height and its association with clinical features; and to determine whether TS patients with acromegaly come from tall families.

Methods: This is a single-center, observational study involving 136 consecutive adult patients with acromegaly and no family history of GH excess. Patients were measured using a stadiometer, while growth data of parents and siblings were collected during the medical interview. Gigantism was defined as either a height which was greater than 3 standard deviations (SD) above the gender- and country-specific mean or greater than 2 SD above MPH. Tall stature was defined as either a height above the 97th percentile for gender- and country-specific data or as a height which was greater than 1.5 SD above MPH.

Results: Thirteen percent (18/136) of acromegaly patients (56% females) met the criteria for gigantism, ten percent (14/136) fulfilled the criteria for TS (57% females). Parents and siblings were not taller than the population mean.

Conclusion: In a group of 136 consecutive patients with acromegaly 24% were taller stature than the population mean; 13% had a gigantism; 10% had TS based on country specific an MPH data. The frequency of gigantism and TS in acromegaly is higher in females than in males. Patients with acromegaly come from normal-stature families.

Abstract-ID: 222

DIAGNOSTIC UTILITY OF BASELINE DEHYDROEPIANDROSTERONE SULFATE (DHEA-S) IN PATIENTS SUSPECTED OF ADRENAL INSUFFICIENCY UNDERGOING ACTH STIMULATION TEST.

Arturo Vega-Beyhart¹, david salas bravo², Mireia Mora³, Manuel Morales-Ruiz⁴, Aida Orois⁵, Maria Montserrat Ruiz⁶, Marta Araujo⁷, Gregori Casals⁸, FELICIA HANZU⁹

¹Hospital Clinic Barcelona/Idibaps, Hospital Ramon Y Cajal Madrid, Endocrinology, Barcelona, Spain

²Hospital Clinic Barcelona, University Barcelona, Endocrinology and Metabolism, Barcelona, Spain

³Hospital Clinic, Hospital Clinic Barcelona, Endocrinology and Metabolism, Barcelona, Spain

⁴Biochemistry and Molecular Genetics Department, Hospital Clínic de Barcelona,, Barcelona, Spain

⁵Hospital Clinic Barcelona, Spain

⁶Hospital Clinic, Spain

⁷Hospital Ramon Y Cajal Madrid, Hospital Ramon Y Cajal, Madrid, Spain

⁸Biochemistry and Molecular Genetics Service , Hospital Clínic de Barcelona,, Centro de Investigación Biomédica En Red de Enfermedades Hepáticas Y Digestivas (Ciberehd), Institut D'investigacions Biomèdiques August Pi I Sunyer (Idibaps), Barcelona, Spain

⁹Idibaps, Endocrinology and Nutrition, Hospital Clinic de Barcelona, Barcelona, Spain, Rossello 149-153, Barcelona, Spain

INTRODUCTION:

Morning cortisol represents the initial marker of choice in the evaluation of suspected adrenal insufficiency (AI) and is subsequently confirmed through the ACTH stimulation test. However, the brief half-life, circadian variability of cortisol, and limited test accessibility pose diagnostic challenges. In light of its superior serum stability and reduced circadian variation, our study aims to assess the diagnostic utility of dehydroepiandrosterone sulfate (DHEA-S) in AI.

METHODS:

We enrolled 92 patients with suspected central or peripheral AI who underwent ACTH stimulation tests between 2014 and 2023 at the Hospital Clinic Barcelona. Baseline DHEA-S, HPA axis, and biochemical biomarkers were measured during the ACTH test.

RESULTS:

Among the patients, 27 were diagnosed with AI based on cortisol levels at 60 minutes after ACTH stimulation ($<18 \mu\text{g/dL}$). The baseline DHEA-S levels in patients with peripheral AI were $0.12 \mu\text{g/dL}$ ($0.05\text{--}0.24$), in those with central AI were $0.16 \mu\text{g/dL}$ ($0.05\text{--}0.39$), and in patients with excluded AI, it was $0.67 \mu\text{g/dL}$ ($0.53\text{--}1.12$) ($p<.001$). DHEA-S exhibited correlations with baseline cortisol ($r=0.47$), cortisol at 30 minutes ($r=0.43$), and cortisol at 60 minutes ($r=0.43$), unaffected by age or gender. Regression analysis identified a logarithmic association between baseline DHEA-S levels and the delta of baseline cortisol/cortisol at 60 minutes during the ACTH test ($R^2=42\%$, $p<.001$). In contrast, baseline cortisol did not exhibit such an association ($r=0.04$). ROC curve analysis demonstrated an AUC of 90% ($p<.001$) for baseline DHEA-S in AI diagnosis, outperforming the AUC of 84% for baseline cortisol. The optimal DHEA-S cutoff values was $0.24 \mu\text{g/dL}$, offering a sensitivity of 82% and specificity of 91%, while a baseline cortisol of $15 \mu\text{g/dL}$ yielded a sensitivity of 44% and specificity of 89%. Specific cutoff points were searched based on gender and age $<<55$ in women case. A DHEA-S level below $0.13 \mu\text{g/dL}$ consistently indicated AI. An sPLS-DA model encompassing age, gender, DHEA-S, and baseline cortisol achieved an AUC of 96% for classifying patients with peripheral, central, or excluded AI ($p<.001$).

CONCLUSION:

Baseline DHEA-S may enhance AI screening by virtue of its stronger association with ACTH test results when compared to baseline cortisol.

Abstract-ID: 243

EARLY PREDICTORS OF REMISSION IN ACROMEGALY PATIENTS AFTER PURE ENDOSCOPIC ENDONASAL TRANSSPHENOIDAL SURGERY

Gamze Akkuş¹, eralp cetinalp², gölşah seydaoğlu³, kerem mazhar özsoy², mevlana akbaba², okay baykara², kadir oktay², tahsin erman²

¹*Cukurova University, Adana, Turkey*

²*Cukurova University, Neurosurgery, Turkey*

³*Çukurova University, Turkey*

Objective: Surgery is the first line treatment in acromegaly however it's still unclear which patients will most benefit. Besides, it takes months to confirm remission. We aimed to evaluate the predictors of remission at the early phase after endoscopic endonasal pituitary surgery in acromegaly patients.

Methods: Fifty-four GH-adenoma patients operated via pure endoscopic endonasal approach were analyzed in this observational study. We compared basic clinical, radiological characteristics, preoperative and postoperative hormone levels in terms of remission according to current guidelines.

Results: The surgical remission rate was 61.1%. When the patients were compared according to surgical remission, the age, gender, immunohistochemical granulation type were non-significant while diabetes mellitus was more common (55.6 vs 44.4%), the preoperative tumor volume ($1.2 \pm 0.9 \text{ cm}^3$ vs $4.1 \pm 4.2 \text{ cm}^3$), postoperative GH and IGF-1 levels were higher in the non-remission group ($p < 0.05$). We defined a number of cut-off values of both GH and IGF-1 levels to predict remission at the postoperative phase. MVA results showed that age [odds ratio (OR): 1.13; 95% confidence interval (95%CI) 1.00-1.27, $p = 0.042$], tumor volume $\geq 1.7 \text{ cm}^3$ (OR: 3.43; 95%CI: 1.13- 10.38, $p = 0.029$; and postoperative day 1 (POD1) GH levels (OR): 9.60; 95%CI: 2.05-44.90, $p = 0.004$) were independent predictors of remission.

Conclusion: We demonstrate that POD1 GH levels, tumor volume and age are independent predictors of remission in acromegaly patients operated via pure endoscopic endonasal technique. POD1 GH levels may be used as an early marker of remission and this may lead to early taking adjuvant medical therapies into account to improve prognosis.

Key Words: Acromegaly, Remission, Pituitary adenoma, Endoscopic endonasal.

Abbreviations: MVA: Multivariate analysis, GH: Growth Hormone, IGF-1: Insuline-like growth factor, POD1GH: Postoperative day 1 growth hormone, MRI: Magnetic resonance imaging, CT: Comupterized Tomography, CSF: Cerebrospinal fluid, ROC: Receiver operational characteristics, AUC: Area under curve, DM: Diabetes Mellitus

Abstract-ID: 246

DYNAMICS OF ANTHROPOMETRIC PARAMETERS IN WOMEN OF CHILDBEARING AGE WITH CUSHING'S SYNDROME AFTER SURGICAL AND DRUG TREATMENT THE PURPOSE OF THE STUDY:

Oydin Irgasheva¹, Zamira Khalimova²

¹*Mirzo-Ulugbek56, Neyroendocrinology, Tashkent*

²*Republican Specialized Scientific-Practical Medical Center of Endocrinology, Republican Center of Endocrinology, Republican Center of Endocrinology, Tashkent, Uzbekistan*

The results obtained allowed the authors to conclude that pathogenetic therapy, leading to stable clinical and hormonal remission of Itsenko-Cushing's disease and weight loss in primary obesity, usually leads to the restoration of the functioning of the reproductive system in such patients. In addition, positive changes in weight also affected the reproductive function of patients: spontaneous restoration of fertility was observed and pregnancy was achieved in patients of group 1 – in 23.0% of cases. Objective: To study the dynamics of anthropometric parameters in women of childbearing age with SC before and 6 months after treatment. MATERIALS AND METHODS OF INVESTIGATION: Transnasal pituitary adenomectomy (TAG) was performed initially in 107 (50.5%) patients with ACTH-KYC, of which 10 (9.3%) were performed secondarily. Adrenalectomy was performed in only 43 (20.3%) patients, including 11 patients with ACTH-CKD. All patients with surgical treatment developed compensation for the condition against the background of HRT. The patients were prescribed non-drug therapy and drug therapy. Non-drug therapy included general recommendations for measuring weight every day before and after exercise therapy, counting daily calories, as well as avoiding easily digestible carbohydrates. Conclusions: Thus, the inclusion of various groups in the traditional treatment of patients with SC in the postoperative period of drug and non-drug treatment contributes to a significant improvement in clinical indicators - a decrease in BMI, which indirectly indicates that in the studied groups of women, obesity is one of the markers of reproductive disorders. The results obtained allowed the authors to conclude that pathogenetic therapy, leading to stable clinical and hormonal remission of Itsenko-Cushing's disease and weight loss in primary obesity, usually leads to the restoration of the functioning of the reproductive system in such patients. In addition, positive changes in weight also affected the reproductive function of patients: spontaneous restoration of fertility was observed and pregnancy was achieved in patients of group 1 – in 23.0% of cases.

Abstract-ID: 247

PRECOCIOUS PUBERTY ASSOCIATED WITH ADRENOCORTICAL CARCINOMA

Dilafroz Uralova¹, Zamira Khalimova²

¹Republican Specialized Scientific and Practical Medical Center of Endocrinology, Scientific, Tashkent, Uzbekistan

²Republican Specialized Scientific-Practical Medical Center of Endocrinology, Republican Center of Endocrinology, Republican Center of Endocrinology, Tashkent, Uzbekistan

Introduction

Precocious puberty has been defined by the development of secondary sexual characteristics before the age of 9 years in boys and 8 years in girls. It is generally estimated to affect 1 in 5000–10,000 children.

Case presentation

A 3-year-old boy presented after a penis enlargement, pubic hair growth, hoarse voice, and enlarged testicles. These complaints started at age 2, and progressed rapidly. From anamnesis, parents are not related, siblings have no such signs. During the examination, he was Tanner stage 3 for axillary and pubic hair. The length of the penis was 6 cm, the volume of the testicles was 5 ml. Serum total testosterone was very high 22,4 nmol/l (normal for age 0,07-1,04 nmol/l); DHEA-S and cortisol were elevated at 25,2 nmol/l (normal for age 0,47-19,4 nmol/l) and at 35,4 mkg/dl (6,2-19,4 mkg/dl) respectively. Electrolytes, aldosterone and renin were normal. Initial abdominal ultrasound and computed tomography revealed a heterogeneous mass in the left adrenal gland 5,5*4,6*7,1 cm. No pathological foci were detected in the CT scan of the chest and small pelvis. A left-sided adrenalectomy was performed. According to pathohistological conclusion, the tumor tissue was found to be adrenocortical carcinoma. He received carboplatin and daily oral mitotane. After 2 chemotherapy cycles, repeat PET-CT scan was found no pathological nodules. X-ray of the left hand showed open growth zones, bone age of 10-11 years. Serum levels of testosterone, DHEA-S and cortisol were normalized within 6 month after surgery and 2 cycles of chemotherapy. The patient was advised to undergo dynamic follow-up at the pediatric endocrinologist and oncologist every 6 month. He remains well at age 7 with no recurrence, secondary malignancy, or new malignancy.

Conclusion

Thorough history and physical examination are critical in diagnosing sexual precocity. In boys with PP, mandatory determination is recommended to study the level of 17-hydroxyprogesterone in the blood to exclude congenital adrenal hyperplasia, to study the level of dehydroepiandrosterone in the blood and/or dehydroepiandrosterone sulfate in the blood to exclude androgen-producing adrenal tumors. If a tumor is identified, staging will include cross-sectional imaging with CT, PET/CT, or MRI of the chest, abdomen, and pelvis, with visualization of lymph nodes.

Abstract-ID: 249

ACROMEGALY MANAGEMENT IN THE NORDIC COUNTRIES – A DELPHI CONSENSUS SURVEY

Mai C. Arlien-Søborg¹, Jakob Dal², Ansgar Heck³, Pia Burman⁴, Jens Otto Jorgensen⁵

¹Aarhus University Hospital, Department of Endocrinology and Internal Medicine, Aarhus, Denmark

²Department of Endocrinology, Aalborg University Hospital, Denmark, Denmark

³Oslo University Hospital, Norway

⁴Skåne University Hospital, Sweden

⁵Aarhus University Hospital, Aarhus, Denmark

Background

Acromegaly is associated with increased morbidity and mortality if left untreated. The therapeutic options include surgery, medical treatment, and radiotherapy. Several guidelines and recommendations on treatment algorithms and follow-up exist. However, not all recommendations are strictly evidence-based.

Aim

To evaluate consensus on the treatment and follow-up of patients with acromegaly in the Nordic countries.

Methods

A Delphi process was used to map the landscape of acromegaly management in Denmark, Sweden, Norway, Finland, and Iceland. An expert panel developed 37 statements on the treatment and follow-up of patients with acromegaly. Dedicated endocrinologists (n=47) from the Nordic countries were invited to rate their extent of agreement with the statements, using a Likert-type scale (1-7). Consensus was defined as $\geq 80\%$ of panelists rating their agreement as ≥ 5 or ≤ 3 on the Likert-type scale.

Results

Consensus was reached in 41% (15/37) of the statements. Panelists agreed that pituitary surgery remains first line treatment. There was general agreement to recommend first-generation somatostatin analog (SSA) treatment after failed surgery and to consider repeat surgery. In addition, there was agreement to recommend combination therapy with first-generation SSA and pegvisomant as second- or third-line treatment. In more than 50% of the statements, consensus was not achieved. Considerable disagreement existed regarding pegvisomant monotherapy, and treatment with pasireotide and dopamine agonists.

Conclusion

This consensus exploration study on the management of patients with acromegaly in the Nordic countries revealed a relatively large degree of variability among experts, which mirrors the complexity of the disease and a shortage of evidence-based data.

Abstract-ID: 261

“FEATURES OF PRE- AND POSTOPERATIVE MAGNETIC RESONANCE IMAGING FOR NONFUNCTIONAL PITUITARY MACROADENOMAS”

Malika Mirtukhtaeva¹, Urmanova Yulduz²

¹Republican Specialized Scientific and Practical Medical Center for Endocrinology of the Ministry of Health of the Republic of Uzbekistan Named Acad. Y.H. Turakulova, Department of Neuro- Endocrinology, Tashkent, Uzbekistan

²Tashkent Paediatric Medical Institute, Republican Scientific-Practical Medical Center of Endocrinology, Scientific, Tashkent, Uzbekistan

INTRODUCTION Unlike functioning pituitary adenomas, which are usually detected quickly due to symptoms of excessive hormonal secretion, detection of nonfunctional pituitary adenomas (NFPA) occurs relatively late. As a result, NFPA is usually found as macroadenomas (1–4 cm) or giant adenomas (>4 cm) with a suprasellar extension that tend to invade the cavernous sinus.

THE PURPOSE OF THE STUDY is to examine the relationship between pituitary function after transsphenoidal surgery and MRI characteristics in inactive pituitary macroadenoma.

MATERIALS AND METHODS OF RESEARCH. The study included 44 patients with inactive pituitary macroadenoma who underwent transsphenoidal surgery. Of these, there were 27 men and 17 women. The average age of men was 46.1 ± 4.2 years, women - 37.5 ± 4.3 years. All patients were treated as inpatients in the neuroendocrinology department in the period 2022-2023 at the Acad. Y.H. Turakulova.

Research methods included: biochemical (bilirubin, direct, indirect, lipid spectrum, ALT, AST, PTI, coagulogram, blood sugar, blood sugar, etc.), hormonal (STH, IGF-1, LH, FSH, prolactin, ACTH, TSH, free thyroxine, cortisol, etc.) and instrumental: ECG, MRI of the pituitary gland, ultrasound of internal organs, fundus.

RESEARCH RESULTS. There was a significant unfavorable relationship between preoperative tumor size and postoperative serum TSH level (odds ratio (OR): - 0.99 (- 0.18, - 0.003), $p = 0.04$). There was also a significant association between preoperative tumor size and postoperative prolactin levels (OR: 5.29 (1.65, 8.92), $p = 0.006$). According to the results of the present study, no normal tissue was observed in 21.4%

Morphological reconstruction of the pituitary gland after surgery is as follows: invisible normal pituitary tissue in 21.4% (9/42) of patients, complete normal pituitary tissue in 45.3% (19/42), partial remnants of normal pituitary tissue in 33.3%. (14/42) patients. There was also a significant unfavorable relationship between preoperative tumor volume and postoperative NOG (OR: 0.99 (0.99, 0.99), $p = 0.007$).

CONCLUSIONS. A significant relationship was found between the size and volume of the preoperative tumor and postoperative mountain production

Abstract-ID: 263

EFFECTS OF ENVIRONMENTAL POLLUTANTS ON AN IN VITRO PITUITARY CELL MODEL

Aurelio Minuti¹, Federica Aliquò², Marily Theodoropoulou¹, Salvatore Cannavò³

¹Ludwig-Maximilians-Universität München, Mediv, München, Germany

²University of Messina, Department of Biomedical and Dental Sciences and Morphofunctional Images, Messina, Italy

³Department of Human Pathology, Endocrine Unit, University Hospital, Dep. of Human Pathology of Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy

Background. Heavy metals such as lead (Pb), manganese (Mn), cadmium including cadmium chloride (Cdc-12), and mercury including methyl mercury (MeHgCl) and mercuric chloride (HgCl₂), are among the most dangerous environmental pollutants for human health. Similarly, pesticides have detrimental effects on human health and many have endocrine disrupting properties, affecting among others pituitary-gonadal and pituitary-somatotroph axes. Their effects on metabolic disorders, obesity, thyroid homeostasis, androgenic and anti-androgenic actions and hypothalamo-pituitary axis have been studied¹. A previous study reported that Cd exposure in rats affects GH, ACTH, and TSH hormone levels².

Aim. The present study aims at investigating the impact of heavy metals and pesticides on pituitary cell viability using GH3 cells as a model.

Methods. GH3 cells were challenged with increasing concentrations of toluene, the pesticides dichlorodiphenyldichloroethylene (4.4 DDE), pentachlorophenol (PCP), α-Lindan and γ-Lindan, and the heavy metals Pb, Cdc-12, HgCl₂ and MeHgCl for 48h. Cell viability was determined with the colorimetric WST-1 assay. Values are means ± SD of 3 experiments and analyzed with One-way ANOVA followed by a Bonferroni's multiple comparison.

Results. GH3 cell viability decreased after exposure to increasing concentrations of Cdc-12 (30% suppression at 11μM compared to control reaching 70% suppression at 100μM) and Pb (42% suppression at 25μM). Exposure to MeHgCl, HgCl₂ and Mn dramatically suppressed cell viability in a dose dependent manner by 97% at 5μM MeHgCl (p<0.05), 93% at 20μM HgCl₂ (p<0.01) and 94% at 4.5μM Mn (p<0.05). Exposure to the pesticides 4.4 DDE, PCP, α-lindan, and γ-lindan decreased GH3 cell viability at low concentrations with 19% suppression at 1.16μM 4.4 DDE, 39% at 9,4 μM PCP, and 49% and 43% suppression at 3.4μM α- and γ-lindan respectively. In contrast, toluene had no effect on GH3 cell viability.

Discussion and conclusion. Using a pituitary cell line, we demonstrate that exposure to heavy metals such as cadmium, mercury, lead and manganese as well as pesticides has severe consequences on pituitary cell viability. It would be interesting to deepen the impact of heavy metals and pesticides on cell viability, pituitary function and stress response in other pituitary cell models.

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Abstract-ID: 264

“ANALYSIS OF RISK FACTORS FOR NODULE FORMATION IN THE THYROID GLAND AND UTERUS IN PATIENTS OF FERTILE AGE”

Zamira Khalimova¹, Nilufar Ishankulova²

¹Republican Specialized Scientific and Practical Medical Center of Endocrinology Named after Academician Yo. Kh.

Turakulov, ²Republican Specialized Scientific Practical Medical Center of Endocrinology of Public Health Ministry Named by Acad. Ya.Kh. Turakulov-, Neuroendocrinology, Tashkent, Uzbekistan

²Republican Specialized Scientific Practical Medical Center of Endocrinology of Public Health Ministry Named by Acad. Ya.Kh. Turakulov-, Ambulance, Tashkent, Uzbekistan

Background. Previous studies have shown that estrogens may play an important role in the formation of thyroid nodules. In addition, it has recently been reported that women with uterine fibroids, which are influenced by estrogen, are more likely to develop thyroid nodules.

The purpose of the study is to identify the relationship between uterine fibroids and thyroid nodules and to find factors that may influence the occurrence of thyroid nodules.

Материал и методы исследования. In the clinic of the Republican Specialized Scientific and Practical Medical Center of Endocrinology of the Ministry of Health of the Republic of Uzbekistan named after Acad. Y.H. Turakulov from 2022 to 2023, 80 women with nodules in the thyroid gland and uterus aged 18 to 44 years were examined. The patients were divided into 3 groups: group 1 – 25 patients with thyroid nodules, group 2 – 27 patients with nodular and hyperplastic processes of the uterus, group 3 – 28 patients with nodules of the thyroid gland and uterus. 20 healthy women made up the control group. All patients underwent hormonal and instrumental studies.

Research results. All groups were dominated by low SES patients and urban residents. Hereditary burden occurred in 13 cases out of 55 observations (23.6%).

The greatest correlation was observed with hereditary burden in group 3 of patients with nodules in the thyroid gland and uterus.

Thus, correlation analysis showed that uterine fibroids are significantly associated with thyroid nodules, but not with hypothyroidism or hyperthyroidism. No association was found with other risk factors.

Conclusions. 1. Our results are consistent with previous studies showing that patients with uterine fibroids have a higher incidence of benign thyroid disease, such as thyroid goiter and thyroid nodules. 2. Our study showed that uterine fibroids are significantly associated with thyroid nodules, but not with hypothyroidism or hyperthyroidism. No association was found with other risk factors.

Abstract-ID: 265

URINE AND SERUM SOLUBLE ALPHA KLOTHO: COMPARISONS OF NON-FUNCTIONING PITUITARY ADENOMA, ACROMEGALY, AND A HEALTHY COHORT

Anica Pauline Gagliardo¹, Michael Haenelt², Júnia Ribeiro de Oliveira Longo Schweizer³, Jun Thorsteinsdottir⁴, Daniel Teupser⁵, Jochen Schopohl⁶, Martin Bidlingmaier⁷, Katharina Schilbach⁸

¹Medizinische Klinik und Poliklinik IV, LMU Klinikum München, Endokrinologisches Labor, München, Germany

²Klinikum der Universität München, Medizinische Klinik und Poliklinik IV, Ludwig Maximilians Universität München; Med. Klinik und Poliklinik IV / Endokrinologie; Medizinische Klinik und Poliklinik IV, Munich, Germany, München, Germany

³LMU Klinikum; Med. Klinik und Poliklinik IV / Endokrinologie; Med. Klinik und Poliklinik IV, Endokrinologisches Labor, Innenstadt, Munich, Germany

⁴University Hospital, Department of Neurosurgery, Germany

⁵Ludwig-Maximilians-Universität München, Institut für Laboratoriumsmedizin, München, Germany

⁶Medizinische Klinik IV, Lmumünchen, LMU Klinikum, München, Neuroendocrinology, Munich, Germany

⁷LMU Klinikum, Med. Klinik und Poliklinik IV / Endokrinologie, Med. Klinik und Poliklinik IV, Munich, Germany

⁸Med. Klinik & Poliklinik IV, LMU Klinikum, Medizinische Klinik und Poliklinik IV, München, Germany

INTRODUCTION:

Soluble alpha klotho (saKL) is a circulating peptide hormone, that can be measured in serum, urine and cerebrospinal fluid and has been shown to correlate with growth hormone excess in serum. There are data, although sparse, suggesting that saKL correlates in urine as well. However, the conditions for measuring urine saKL remain challenging: while it is possible to store urine at -80°C, other preanalytical aspects need to be evaluated to determine whether urine saKL can be utilized as a biomarker. Previous smaller pilot studies suggest that urine saKL is markedly higher in patients with acromegaly compared to patients with non-functioning pituitary adenomas (NFPAs) where saKL was not measurable. Since studies on urine saKL show instabilities and the mentioned study reported technical aspects that need to be clarified, we sought to further evaluate the conditions necessary to utilize urine saKL as a reliable biomarker.

METHODS:

We collected spontaneous urine and serum samples along with anthropometrical data from 15 healthy subjects (control group), 8 patients each with acromegaly and NFPA. Urine and blood samples were stored at -80°C and -20°C, respectively. SaKL was measured with a sandwich ELISA (IBL, Hamburg).

RESULTS:

In the control group, after storage at -80°C, mean saKL was 2661 and 640 pg/mL for urine and serum, respectively. The mean was 533 and 1948 pg/ml, respectively, for urine and serum samples from patients with acromegaly. Contradicting the few existing data from the literature so far, saKL was measurable in all NFPA urine samples with a mean concentration of 3364 pg/mL. In the corresponding serum samples mean saKL was 962 pg/mL. A positive correlation between urine saKL and pH could be shown (Pearson's r 0.591, $p < 0.001$).

DISCUSSION:

Contrary to previous studies, we were able to show that measurement of saKL in urine samples of NFPA patients is possible. Furthermore, and well acquainted with the fact that it is a small number of NFPA patients, urine saKL was not lower than in patients with uncontrolled acromegaly. On the contrary, urine saKL was unexpectedly low in the acromegaly group. However, larger sample sizes are needed to determine whether urine saKL is an appropriate biomarker and therefore further expansion of this study is planned. Moreover, evaluation of the impact of pH on urine saKL needs to be addressed, as it is possible that urine pH poses an additional difficulty in utilizing urine saKL as a biomarker. At this point, we believe that further investigations are necessary before the potential of urine saKL as a biomarker can be determined.

Abstract-ID: 266

"FEATURES OF OVARIAN INSUFFICIENCY IN HYPOTHYROIDISM IN PATIENTS OF FERTILE AGE WITH HYPOTHYROIDISM"

Dildorakhon Gafurova¹, Zamira Khalimova²

¹Andijan State Medical Institute, Tashkent, Uzbekistan

²Republican Specialized Scientific and Practical Medical Center of Endocrinology Named after Academician Yo. Kh.

Turakulov, 2Republican Specialized Scientific Practical Medical Center of Endocrinology of Public Health Ministry Named by Acad. Ya.Kh. Turakulov-., Neuroendocrinology, Tashkent, Uzbekistan

Background. Decreased ovarian reserve (DOR) characterizes women of reproductive age who have regular menstruation, but whose response to ovarian stimulation is reduced compared to women of comparable age. Women with ODS make up ~24% of the infertile population, and their treatment remains a challenge for clinicians.

The purpose of the study is to study ovarian failure in hypothyroidism in patients of fertile age with hypothyroidism.

Material and research methods. The study retrospectively analyzed the results of examination and treatment of 67 women of reproductive age (18-44 years) with subclinical hypothyroidism (SH, n=32) and manifest hypothyroidism (MH, n=35). Women were divided into three groups: 1) low ovarian reserve (women with AMH below 0.3 ng/ml), 2) average ovarian reserve (women with AMH from 0.3 to 3 ng/ml) and 3) normal ovarian reserve (women with AMH above 10 ng/ml). 20 healthy individuals formed the control group

Research methods: collection of clinical data, study of hormones as well as ultrasound of the uterus and ovaries on the 14th day of the cycle.

Research results. In patients with SH, low ovarian reserve was observed in 12 (37.5%) cases, while in patients with MH – in 27 (77.1%). Average ovarian reserve was also more common in the group with SH - 15 (46.8%), and in the group with MH - 6 (17.1%). Normal ovarian reserve was observed in the SH group in 5 observations (15.6%), and in the MH group – in 2 (6.3%).

The groups with SH and MH were significantly different from each other in serum hormone values. TSH levels were significantly higher in the group with MH ($p<0.05$), and the average values of free thyroxine were significantly lower in the group with MH ($p<0.05$). At the same time, the values of antibodies to TPO in both groups did not differ significantly and were within normal limits. The group with low ovarian reserve had the most pronounced hormonal disorders.

Conclusions. The groups with SH and MH differed significantly from each other in the values of serum hormones. Thus, TSH levels were significantly higher in the group with MH ($p<0.05$), and the average values of free thyroxine were significantly lower in the group with MH ($p<0.05$). At the same time, the values of antibodies to TPO in both groups

Abstract-ID: 268**FEATURES OF TYPE 2 DIABETES IN PATIENTS WITH COVID-19**Abdurasul Daminov¹, Gulzoda Negmatova²¹Samarkand State Medical University, Endocrinology, Samarkand, Uzbekistan²Samarkand State Medical University, Samarkand State Medical University, Endocrinology, Samarkand, Uzbekistan

In 2020, the world faced an unprecedented health challenge associated with the invasion of the novel coronavirus SARS COV-2. The collision of two global pandemics – COVID-19 and type 2 diabetes (T2DM) – has led to dismal results: T2DM is the second most common comorbidity in COVID-19. The combination of diabetes, obesity and hypertension increases the risk of death by almost 5 times. COVID-19 is a predictor of diabetes mellitus; therefore, in patients with type 2 diabetes mellitus who have recovered from COVID-19, the incidence of late complications increases.

Purpose of the study. To study the features of the course of type 2 diabetes mellitus with COVID-19.

Materials and methods of research. Patients will be examined according to the program, 20 patients with type 2 diabetes mellitus with Covid and 20 patients with type 2 diabetes mellitus without Covid and 20 control group. Biochemical blood test (glycated hemoglobin, Lipid spectrum). Immunological method - SARS CoV-2 IgM, IgG. Clinical and instrumental - SPO₂, A/D monitoring.

Results: According to the data received glycemic profile in group 1 there are higher levels of glycemia on an empty stomach and two hours after meals; before bedtime, patients in this group have glycemia almost 1.5 times higher than in patients in group 2. Group 1 of patients had a glycemic profile within normal limits. Analysis of the lipid spectrum gave us the following indicators: in group 1 patients, the level of total cholesterol in the blood exceeded the norm by almost 2 times, and in patients in group 2 the same indicator was lower and closer to normal. In the control group it was determined within normal limits. HDL in group 1 of patients averaged 3.1 mmol/l, in group 2 – 2.2 mmol/l, and in the control group within normal limits. LDL in the 1st group of patients averaged 4.9 mmol/l, in the second group - 4.1 mmol/l, and in the control group within normal limits. The study showed that the level of D-dimer in patients in group 1 was almost 3 times higher than the norm; in group 2, the indicator was characterized by a slightly noticeable shift in the level of D-dimer. And in the control group this indicator was within the normal range.

Conclusion: High levels of glycemic profile, D-dimer, LDL in patients with SARS-CoV-2 infection and type 2 diabetes mellitus are the main predictor of complications of the respiratory and cardiovascular systems.

Abstract-ID: 269

FEATURES OF TYPE 2 DIABETES MELLITUS IN COMBINATION WITH ARTERIAL HYPERTENSION AND WAYS FOR THEIR CORRECTION

Dildora Salimova¹, Gulzoda Negmatova²

¹Samarkand State Medical University, Endocrinology, Samarkand, Uzbekistan

²Samarkand State Medical University, Samarkand State Medical University, Endocrinology, Samarkand, Uzbekistan

The clinical and social significance of arterial hypertension (AH) and diabetes mellitus (DM) is determined by their significant contribution to the structure of cardiovascular mortality and the increased risk of developing serious complications when they are combined. Currently, there is a steady increase in the number of patients suffering from diabetes. The incidence of diabetes increases annually by 6-10%. Currently, in the month of September 2019, according to WHO, there are 425 million patients with diabetes mellitus all over the world, and in Uzbekistan over the past 10 years, the number of patients has more than doubled and 202,998 patients with diabetes mellitus are registered.

Purpose of the study: To study the clinical and functional features of arterial hypertension in patients with type 2 diabetes mellitus, depending on the treatment method.

Materials and research methods: 60 patients with type 2 diabetes mellitus in combination with hypertension aged 40-70 years, undergoing inpatient and outpatient treatment at the Samarkand branch of the Russian Scientific Research Center for Emergency Medicine. The study used clinical, biochemical, clinical and laboratory studies, instrumental methods and statistical methods.

Results: All patients were prescribed initial antihypertensive therapy with ACE inhibitors - Enalapril and SGLT-2 inhibitors - Empagliflozin; if a syndrome of tolerance to monotherapy was detected, a combination of these drugs was prescribed. Among patients receiving monotherapy with SGLT-2 inhibitors, there were grade I hypertension - 27 people (26%), grade II hypertension - 44 (40%), grade III hypertension - 23 (20%) and ISAH - 14 (10%), in combinations with ACE inhibitors and SGLT-2 inhibitors: grade I hypertension - 24 (21%), stage II hypertension - 51 (43%), stage III hypertension - 26 (23%) and ISAH - 15 (13%) people. As our results showed, a significant decrease in blood pressure was observed when taking both drugs already 1-2 weeks after the start of therapy. This circumstance should not be regarded as a pharmacokinetically prescribed period of drug accumulation, since in patients with type 2 diabetes the hypotensive effect of empagliflozin and enalapril was observed almost from the first days of their use. Therefore, the period of silent ineffective use of empagliflozin and enalapril can be considered as a kind of marker of endothelial dysfunction.

Conclusion. High clinical effectiveness of the combined approach to prescribing hypoglycemic and antihypertensive therapy with SGLT-2 drugs and ACE inhibitors in patients with concomitant pathology was noted, depending on the level of blood pressure and glycemia, taking into account the principles of chronotherapy.

Abstract-ID: 274

STUDY OF CLINICAL AND BIOCHEMICAL INDICATORS OF LABORATORY ANIMALS WITH AN EXPERIMENTAL MODEL OF ALLOXAN DIABETES

Gulnora Togaeva¹, Gulzoda Negmatova²

¹Samarkand State Medical University, Endocrinology, Samarkand, Uzbekistan

²Samarkand State Medical University, Samarkand State Medical University, Endocrinology, Samarkand, Uzbekistan

The purpose of the work is to study carbohydrate metabolism and biochemical parameters of laboratory animals with a model of alloxan diabetes.

Material and methods. The study was conducted on 30 male Wistar rats weighing 220 ± 20 g, divided into 2 equal groups: a group of intact animals and a group with experimental DM (ED). ESD was induced by a single intraperitoneal injection of alloxan 100 mg/kg. The animals were kept under standard vivarium conditions. at a temperature of $23 \pm 3^\circ\text{C}$, humidity $45 \pm 5\%$, lighting - day/night mode: from 7.00 to 19.00. The animals had free access to water and food.

2 weeks after the administration of diabetogens, whole blood in an amount of 10 ml was taken from the tail vein of the animals, and a clinical blood test was performed using laboratory methods.

Research results. After the administration of alloxan tetrahydrate at a dose of 100 mg/kg, changes in the hormonal and biochemical parameters of the blood serum of rats to the diabetogenic effect of alloxan were observed. The first signs of diabetes manifested themselves in the form of a sharp increase in water consumption to 120 ml, polyphagia, polyuria, hyperglycemia, sudden weight loss, and hair loss. Blood glucose in intact animals was 6.4 ± 0.1 mmol/l, and in experimental animals DM (ESD) was 27.5 ± 2.6 mmol/l. During our study, the activity of alanine aminotransferase in intact animals was 257.0 ± 14.5 units/g, and in the experimental group it was 481.5 ± 49.6 units/g, and the activity of aspartate aminotransferase in intact animals was 476.8 ± 23.8 units/g, and in the experimental group it was 587.4 ± 59.7 units/g.

During experimental exposure to the diabetogenic alloxan, changes in lipid metabolism parameters are observed compared to the control group of animals. Moreover, if serum cholesterol in control animals was 1.97 ± 0.10 , then this figure in experimental animals was 2.59 ± 0.16 , which is two times more than in control animals. It should be noted that glucosuria in experimental animals increased sharply on the first day and remained consistently high until the end of the experiment.

Thus, based on the results of the experiment, it can be noted that animals in the experimental group with alloxan diabetes showed signs of an inflammatory process in the pancreatic parenchyma, which affected the biochemical parameters of the blood serum. In particular, the concentration of glucose in the blood serum of experimental rats with diabetes was more than 4 times higher than in the control group of animals. Simulation of diabetes led to a noticeable increase in the main biochemical parameters.

Abstract-ID: 275

CLINICAL AND BIOCHEMICAL INDICATORS OF OBESITY IN WOMEN OF FERTILE AGE

Mokhichekhra Namozbaeva¹, Gulzoda Negmatova²

¹Samarkand State Medical University, Endocrinology, Samarkand, Uzbekistan

²Samarkand State Medical University, Samarkand State Medical University, Endocrinology, Samarkand, Uzbekistan

The purpose of the study: to study the characteristics of the clinical course of obesity in women of fertile age and to develop a diagnostic algorithm.

Research materials and methods: Our research object consisted of 85 women of fertile age, and we studied them in 3 groups:

Group I - 30 obese women of fertile age with polycystic ovary syndrome

Group II - 30 obese women of fertile age without polycystic ovary syndrome

Group III - control group

According to the results of clinical and biochemical analysis, the following were determined:

According to hormone analyzes of obese women of fertile age with polycystic ovary syndrome belonging to the first group, LH (luteinizing hormone) was equal to 0.103 ± 0.09 IU/L in 17%, i.e. 5 women, that is, slightly lower than the norm, we can see that in 20%, that is, in 6 women, it was 23.74 ± 29.46 IU/L, that is, it exceeded the norm. FSH (follicle stimulating hormone) increased by 20%, that is, in 6 women, it increased to 37.36 ± 3.44 IU/L. Progesterone hormone decreased to 0.63 ± 0.32 ng/ml in 80% (24) women. We can observe that prolactin hormone increased to 417 ± 403 IU/L (norm 66-490) in 77% of women (23).

In the second group of women without polycystic ovary syndrome, FSG hormone increased to 40.8 IU/L in 3% of patients, i.e. in 1 patient. It was observed that DGEAS exceeded the norm in 3% of patients, i.e. in 1 woman. We can observe that the HOMA index increased to 3.29 ± 1.41 in 40% of patients, i.e. in 12 women. It was found that the above indicators in women of the control group belonging to the third group are normal.

Discussion of the results: Hormonal analyzes of obese women of fertile age with polycystic ovary syndrome belonging to the first group showed an increase in FSH, LH hormones due to a decrease in ovarian function. Hormonal analyzes of obese women without polycystic ovary syndrome, belonging to the second group, showed an increase in only the index HOMA (insulin resistance). We can conclude from this that the insulin resistance found in the majority of obese women of fertile age is not related to polycystic ovary syndrome.

Abstract-ID: 278

AGRESSIVE PITUITARY METASTASIS OF LUNG ADENOCARCINOMA CONDITIONING REPEATED PITUITARYAPOPLEXY - CASE REPORT

João Meira Gonçalves¹, Diana Lucas², Manuel Pinto³, Jorge Pedro³, Davide Carvalho³, Josué Pereira³

¹*Centro Hospitalar Universitário de São João, Neurosurgery, Neurosurgery, Porto, Portugal*

²*Centro Hospitalar Universitário São João, Portugal*

³*Centro Hospitalar Universitário de São João, Portugal*

A 57-year-old man presented with increasing headache for the last month and recent onset ptosis of the right eye. He was a life-long smoker. Neurological examination revealed bi-temporal field defects with partial III nerve palsy on the right side, with normal visual acuity. His serum T4 and morning cortisol was 0.62 mU/l (N: 0.7-1.48) and 5.6 mU/l (N: 6.2-19.4), respectively. Former CT scan and MRI showed a sellar mass with compression of the optic chiasm without clear signs of hemorrhage. The patient subsequently underwent an endonasal transsphenoidal exploration with resection of the pituitary lesion. The definite histopathology report revealed fragments of lung adenocarcinoma. Thoracic Computer Tomography confirmed a right lung mass (Stage IV (T3N3M1)). Subsequently, he was admitted again with signs of acute encephalopathy and imaging showed acute pituitary mass enlargement with signs of active hydrocephalus, and a new episode secondary postoperative apoplexy. He was managed with ventriculoperitoneal shunt and, later, whole brain radiotherapy followed by chemotherapy with carboplatin and pemetrexed. Pituitary metastasis portrayed a poor prognosis, early diagnosis and treatment are essential. This patient died 6 months later.

Abstract-ID: 279

LATE PITUITARY APOPLEXY DURING TREATMENT OF MACROPROLACTINOMA IN AN ADOLESCENT – CASE REPORT

Diana Lucas¹, joao meira², Manuel J. Ferreira-Pinto³, Jorge Pedro⁴, Davide Carvalho⁵, Josué Pereira⁶

¹*Centro Hospitalar Universitário de São João, Neurocirurgia, Porto, Portugal*

²*Centro Hospitalar Universitário de São João, Porto, Portugal*

³*São João University Hospital Center, Neurosurgery, Porto, Portugal*

⁴*Centro Hospitalar Universitário de São João, Endocrinologia, Porto, Portugal*

⁵*Chus João, Faculty of Medicine, I3s University of Porto, Porto, Portugal*

⁶*Department of Neurosurgery, Centro Hospitalar São João, E.P.E., Neurosurgery, Porto, Portugal*

We present a case of a 16 years old adolescent male with complains of blurred vision of the right eye, with 6 days of evolution. Neurological examination revealed a Marcus Gunn pupil on right eye. Decreased visual acuity was confirmed by ophthalmologic examination.

A brain MRI (magnetic resonance imaging) scan showed a large sellar lesion with suprasellar extension, probably a macroadenoma, with a right-side predominance and deviation of the optic chiasm superiorly. Diagnosis of macroprolactinoma was made based on serum prolactin levels - 660 ng/ml (normal range: 4.8 – 23.3 ng/ml). No other hormonal alterations were detected.

Medical treatment with cabergoline (1 mg, 2 times a week) was started and a good clinical, biochemical and imaging response was achieved after 2 months: rapid resolution of the visual disturbance, decreased of prolactin levels (660 ---> 35 ng/ml) and reduction of the lesion volume (9 cc ---> 7 cc).

During de follow up, approximately 1 year after the diagnosis, the patient developed complains of severe headache, waking the patient during sleep, without visual disturbance. Brain MRI scan showed enlargement of lesion and signs of acute hemorrhage (apoplexy). Since the headache was refractory to medical therapy, the patient was submitted to endoscopic endonasal transsphenoidal surgery with clinical improvement.

In the presence of acute visual disturbance, surgical decompression may be the initial approach for the treatment of macroprolactinoma. In this case, based on patient's age and surgical risk, the first line of treatment of prolactinoma was medical therapy.

Even with good response with medical therapy, macroprolactinomas should be closely followed by neurosurgery.

Abstract-ID: 283

ENDOCRINOLOGICAL SERVICE IN OBESITY OF SAMARKAND REGION CURRENT STATUS AND DEVELOPMENT PROSPECTS

Aziza Davranova¹, Gulzoda Negmatova²

¹Samarkand State Medical University, Samarkand State Medical University, Samarkand, Uzbekistan

²Samarkand State Medical University, Samarkand State Medical University, Endocrinology, Samarkand, Uzbekistan

Purpose of the study: To assess the prevalence of obesity among the adult population in the Samarkand region depending on gender and age for 2017-2021.

Materials and methods: The work was carried out based on the results of processing the annual statistical reports of the Ministry of Health of the Republic of Uzbekistan (form No. 13) from 2017 to 2021. Anthropometric examination was carried out according to standard methods with measurement of body weight and body length, followed by calculation of body mass index. Body weight was considered overweight with an index of 25.0–29.9 kg/m², obesity – ≥30 kg/m². The sample was formed from persons aged from 20 to 55 and older.

Results. The work was carried out based on the results of processing the annual statistical reports of the Ministry of Health of the Republic of Uzbekistan (form No. 13) from 2017 to 2021. The work surveyed 61,583 persons of both sexes (Table 2), of which 23,129 were men (37.5% of the total number surveyed) and 38,454 women (62.5%).

The prevalence of overweight among the adult population of the Samarkand region, obesity - 35.2%, overweight - 32.6%. Obesity was more common among men - 37.5%; obesity was 62.5% more common among women. The prevalence of class I obesity was 55.5%. II and III degrees – 34.15 and 10.35%, respectively.

During the examination, 55.5% of patients had grade I obesity; no significant changes in health status were observed, even the figure did not change much, the body mass index ranged from 30.0 to 34.9. The patients had complaints, fatigue, increased drowsiness, excessive sweating, unmotivated irritability and nervousness. Occasionally increased blood pressure.

Patients with II degree obesity 34.15% body mass index 35.0 – 39.9, they had complaints against the background of which body weight increases by 30 – 40% weakness increases, pain and “ache” in large joints, constant pain in the lower back, stiffness of the back muscle corset in the area of the shoulder blades and collar area, instability of blood pressure, throbbing headaches, swelling of the lower extremities and fingers.

III degree of obesity 10.35% body mass index exceeds 40 and actual weight is 50 - 99% higher than normal. Patients complain of progressive hypertension, tachycardia, shortness of breath not only during physical activity, but also at rest, pain in the ankle, knee joints, swelling of the face and upper extremities. And in women, menstrual irregularities affect potency.

Conclusion: The study showed a high prevalence of overweight and obesity among the adult population of the Samarkand region.

Abstract-ID: 286

PITUITARY STALK INTERRUPTION SYNDROME IN A 14-MONTH OLD CHILD: CASE REPORT OF A RARE CAUSE OF ABNORMAL SHORT STATURE

Manuel J. Ferreira-Pinto¹, Diana Lucas², João Meira Gonçalves³, Rita Santos Silva⁴, Josué Pereira⁵

¹*São João University Hospital Center, Neurosurgery, Porto, Portugal*

²*Centro Hospitalar Universitário de São João, São João University Hospital Center, Neurocirurgia, Porto, Portugal*

³*Centro Hospitalar Universitário de São João, Neurosurgery, Neurosurgery, Porto, Portugal*

⁴*São João University Hospital Center, Pediatrics, Portugal*

⁵*Department of Neurosurgery, Centro Hospitalar São João, E.P.E., Neurosurgery, Porto, Portugal*

Introduction:

Pituitary stalk interruption syndrome (PSIS) is a rare congenital disorder affecting 0,5 per one million births, with poorly understood etiological mechanisms. It is defined by the triad of absent or hypoplastic anterior pituitary, thin or absent infundibulum and absent or ectopic posterior pituitary and can lead to early-life pan-hypopituitarism and death.

Case report:

We hereby describe the case of a 14-month old child, who presented with failure to thrive (growth between percentiles 3 and 15). Born from an eutocic delivery after an uneventful 40-weeks gestation, she was otherwise healthy. Parents report feeding difficulties due to nasal obstruction but no diarrhea or frequent infections. No major craniofacial or body abnormalities were evident on examination. Blood tests revealed low IGF1 levels and central hypothyroidism, with normal cortisol axis tests and normal osmolarity. These findings lead to a pituitary MRI which revealed an hypoplastic anterior pituitary, absent pituitary stalk and absent posterior pituitary. Levothyroxine treatment was started, and genetic test is ongoing.

Conclusion:

Despite its rare occurrence, PSIS must be considered in children with failure to thrive. The present work aims at raising awareness for this entity, as a high level of suspicion is required to identify this disorder. Early detection is crucial in order to promptly start hormone replacement therapy and to prevent the low-quality and life-threatening state of pan-hypopituitarism.

Abstract-ID: 287

"NEUROCOGNITIVE DYSFUNCTION IN WOMEN WITH FUNCTIONAL HYPERPROLACTINEMIA"

Adliya Kholikova¹, Nargiza Khalimova²

¹Republican Specialized Scientific and Practical Medical Center of Endocrinology Uzbekistan, Republican Specialized Scientific and Practical Medical Center of Endocrinology of the Ministry of Health of the Republic of Uzbekistan Named after Academician. Y.H. Turakulov,, Department of Neuroendocrinology,, Tashkent, Uzbekistan

²Republican Specialized Scientific and Practical Medical Center of Endocrinology of the Ministry of Health of the Republic of Uzbekistan Named after Academician. Y.H. Turakulov, Department of Neuroendocrinology,, Tashkent, Uzbekistan

Background. Screening tests play a critical role in the diagnosis of neurocognitive impairment, so they must be very sensitive to assess mild cognitive impairment (MCI). Currently, the Mini-Mental State Examination (MMSE) is the most commonly used scale to assess cognitive function, although it is claimed to be inaccurate in identifying MCI. The Montreal Cognitive Assessment (MoCA) was created as an alternative to the MMSE. At the same time, in patients with hyperprolactinemia (HPRL), such studies were performed in isolated studies.

The purpose of the study is to study neurocognitive disorders in women of fertile age with functional hyperprolactinemia

Material and research methods. 60 patients of fertile age with functional HPLC syndrome were examined. The age of the patients ranged from 25 to 45 years and averaged 34±6.5 years.

Based on the average prolactin level, the patients were divided into 2 groups: group 1 – up to 30 ng/ml (30 patients); Group 2 – from 30 to 50 ng/ml (30 patients); The comparison group consisted of 20 healthy women of fertile age.

The patients underwent general clinical, anthropometric, biochemical, hormonal and instrumental research methods.

Research results. It was found that 17 patients with HPLC (28.3%) patients had MCI by both MMSE and MoCA, while 3 patients (5%) whose MMSE tests were normal tested positive for MCI using MoCA . Of the entire studied sample, 40 out of 60 patients (66.7%) had normal scores on both tests.

Significant trends in increasing MCI prevalence were observed along with increasing prolactin values according to both MMSE and MoCA. At the same time, a direct correlation was observed between the level of PRL and the degree of CD.

Conclusions 1. Significant trends of increasing MCI prevalence were observed along with increasing prolactin values according to both MMSE and MoCA. 2. The results of this study showed that MMSE and MoCA had a good correlation for identifying MCI in women aged 18 to 44 years with hyperprolactinemia.

Abstract-ID: 288

“FEATURES OF HORMONAL DISORDERS IN CHILDREN WITH NODULES IN THE THYROID GLAND”

Adliya Kholikova¹, Gulchekhra Saidova²

¹Republican Specialized Scientific and Practical Medical Center of Endocrinology Uzbekistan, Republican Specialized Scientific and Practical Medical Center of Endocrinology of the Ministry of Health of the Republic of Uzbekistan Named after Academician. Y.H. Turakulov,, Department of Neuroendocrinology,, Tashkent, Uzbekistan

²Medical Association of Kitab District Kashkadarya Region, Kitab, Uzbekistan

Background. Thyroid nodules in children and adolescents represent a serious diagnostic problem. Although thyroid nodules are relatively rare in children compared to adults, they require careful evaluation due to the increased risk of malignancy.

The purpose of the study is to study the hormonal characteristics of children with nodules in the thyroid gland.

Material and research methods. 68 children with nodule formation aged 3 to 9 years were examined. In total there were 35 boys and 33 girls. The patients were divided into 3 groups: gr. 1 – children with a thyroid nodule up to 1 cm – 32 patients, gr. 2 – children with a thyroid nodule from 1 to 2 cm (or multiple nodes) – 19 people, gr. 3 – children with a thyroid nodule more than 2 cm (or multiple nodes) 17 patients. 20 healthy children made up the control group.

All patients underwent the following studies: hormonal (TSH, free thyroxine, antibodies to TPO, growth hormone, prolactin), instrumental methods as well as anthropometry.

Research results. In total, among 68 children, a state of subclinical hypothyroidism was detected in 30 (44.1%) patients, and manifest hypothyroidism in 12 (17.6%) patients.

In patients of groups 1 and 2, there was an unreliable decrease in basal values of LH and FSH ($p < 0.05$) compared to the control group against the background of moderate hyperprolactinemia and a significant increase in average TSH values.

In patients of gr. 3, there was a significant decrease in basal values of LH and FSH ($p < 0.05$) compared to the control group, as well as significantly low levels of free testosterone (FT) in blood plasma in boys ($p < 0.05$) against the background of moderate hyperprolactinemia and a significant increase in average TSH values. These disorders correspond to the presence of hypogonadotropic (secondary) hypogonadism.

Conclusions. 1. Among 68 children, a state of subclinical hypothyroidism was detected in 30 (44.1%) patients, and manifest hypothyroidism in 12 (17.6%) patients. In total, 42 patients out of 68 adolescents examined suffered from hypothyroidism. 2. In groups 1 and 2, the levels of TSH and free thyroxine corresponded to the state of subclinical hypothyroidism, while in group 3 - manifest hypothyroidism

Abstract-ID: 289

"CLINICAL AND IMAGING CHARACTERISTICS OF PATIENTS WITH NODULAR AUTOIMMUNE THYROIDITIS ACCORDING TO REFERRAL DATA"

Dildora Kenjaeva¹, Adliya Kholikova²

¹*Kashkadarya Branch Rsnpmce Ministry of Health of the Republic of Uzbekistan Named after Academician. Y.H. Turakulov, Karshi, Uzbekistan*

²*Republican Specialized Scientific and Practical Medical Center of Endocrinology Uzbekistan, Republican Specialized Scientific and Practical Medical Center of Endocrinology of the Ministry of Health of the Republic of Uzbekistan Named after Academician. Y.H. Turakulov,, Department of Neuroendocrinology,, Tashkent, Uzbekistan*

Background. AIT is the most common autoimmune endocrine disease, with a prevalence estimated at approximately 3-5% of the general population. AIT predominantly affects women, and its incidence increases with age. Nodular AIT is a risk factor for the development of a tumor process in the thyroid gland.

The purpose of the study is to study the clinical and imaging characteristics of women of fertile age with nodular autoimmune thyroiditis.

Material and methods of research: 56 women of fertile age (prospectively) with nodular AIT were examined in 2023. The average age of the patients was 31.2 ± 5.2 years. 20 healthy women of the appropriate age formed the control group.

Research methods - general clinical, biochemical, hormonal and instrumental.

Research results. In patients with nodulation in the thyroid gland, the location of nodes dominated in the upper part - 30 (53.5%) cases, and in the lower part there were 11 (19.6%) cases of node location. In 2 cases, we identified nodes with suspected malignancy at an early stage of examination (TIRADS 4 - suspicious for malignant changes in the thyroid gland.).

In the main group, symptoms of primary hypothyroidism dominated against the background of high antibodies to TPO, TG and pT ($p < 0.001$). The average TSH values in the main group of patients corresponded to the state of manifest hypothyroidism ($p < 0.005$).

The structure of the thyroid gland itself was normal in 12 cases, hypoechoic in 18 cases, and hyperechoic in 26 cases. In 32 (57.1%) patients, the thyroid structure was heterogeneous, and in 19 (33.9%) there were hypoechoic nodules.

Histopathological evaluation revealed that in 2 cases a malignant thyroid tumor was detected. But these formations were not encapsulated. All patients had visible lymphocytic infiltration around the tumor.

Conclusions. A malignant thyroid tumor (2 cases) was detected at an early stage using ultrasound before performing FNA. We found that in these cases the growth rate of thyroid nodules was very high: a doubling or tripling of growth was observed over a period of 2-6 months of observation.

Abstract-ID: 290

FREQUENCY OF ACCOMPANYING PATHOLOGY IN PATIENTS WITH AUTOIMMUNE POLYGLANDULAR SYNDROME INVOLVING ENDOCRINE GLANDS AND NON-ENDOCRINE ORGANS

Gulzoda Negmatova¹

¹*Samarkand State Medical University, Samarkand State Medical University, Endocrinology, Samarkand, Uzbekistan*

Autoimmune adult polyglandular syndrome (APS) is characterized by damage to two or more endocrine glands, most often leading to the development of their hormonal deficiency. The basis of most autoimmune endocrine diseases is lymphoid and macrophage infiltration of the target organ.

Purpose of the study: To study the clinical features of patients with APS type 2 with manifest damage to the endocrine glands (thyroid, pancreas, adrenal glands and non-endocrine organs - RA and vitiligo) in people of Uzbek nationality in a comparative aspect.

Materials and research methods: The study was carried out at the bases of the Republican Scientific and Practical Medical Center of the Ministry of Health of the Republic of Uzbekistan and at the Samarkand Regional Endocrinological Dispensary during 2015-2021. Our study included 188 patients, divided into 2 groups: the 1st main group consisted of 118 patients with damage to the endocrine glands (type 1 diabetes, PCNN, AIT), the 2nd group included 70 patients with autoimmune pathology with damage to non-endocrine organs.

Research results: In patients of the main group, specific symptoms of damage to the endocrine glands such as weight loss, hypotension, and sexual dysfunction occurred with a high frequency. Moreover, 1/3 of the patients had arthralgia with morning stiffness up to 15.6%, melasma in 100% of patients with PCNN, and vitiligo-like spots in 10% of patients with type 1 diabetes. At the same time, clinical manifestations of patients with non-endocrine lesions, in addition to rheumatoid arthritis and vitiligo, included endocrine disorders in the form of decreased sexual function in 44.3%, weight loss in 11.4% and proximal myopathy in 75.7% of cases. We analyzed concomitant diseases by group. In the first group, the 1st place among concomitant diseases was anemia - 51 observations out of 118 (38.8%), the 2nd place was allergic diseases - 38 cases (20.2%), the 3rd place was hypothyroidism - 34 observations (18.09%) and, finally, in 4th place - asthenoneurotic syndrome - 32 patients (17.02%), which is 2 times more than in patients of the second group. In patients of the second group, anemia was also dominant - 22 cases out of 70 (31.43%), rheumatism - 19 cases out of 70 (27.14%).

Conclusions: Thus, in patients with endocrine manifestations of APS type 2, the associations most often observed were anemia (25.4%), allergic diseases (18%) and hyperurecemia (18.6%). In non-endocrine manifestations of APS, anemia also predominated (31.4%), although the cases of chronic pyelonephritis (25%) and hyperurecemia, chronic pancreatitis (11.9%), and chronic hepatitis (15%) were significantly higher.

Abstract-ID: 291

"BRAIN-DERIVED NEUROTROPHIC FACTOR BDNF IN PATIENTS WITH TYPE 2 DIABETES MELLITUS ON HEMODIALYSIS"

Alisher Kholikov¹, Urmanova Yulduz²

¹Republican Specialized Scientific and Practical Medical Center of Endocrinology of the Ministry of Health of the Republic of Uzbekistan Named after Acad. Y.H. Turakulov,, Hemodialysis Department,, Tashkent, Uzbekistan

²Tashkent Paediatric Medical Institute, Republican Scientific-Practical Medical Center of Endocrinology, Scientific, Tashkent, Uzbekistan

Background. BDNF is being actively studied to determine the prognosis and severity of stroke, as well as cognitive impairment in various diseases, including diabetic polyneuropathy. In patients with DM2 and stage 5 chronic kidney disease (CKD) with or without hemodialysis, it has not yet been studied in the domestic and foreign literature.

The aim of study: to evaluate the value of determining the BDNF in patients with DM 2 and CKD 5 st.

Material and research methods. We examined 150 patients with CD2 type, suffering from stage 5 CKD, who were on program hemodialysis. Of these, there were 55 women and 95 men. The average age of men was 67 ± 4.2 years, and the average age of women was 64 ± 5.6 years

According to the degree of chronic cerebral ischemia (CCI), patients were divided into 3 groups: 1 gr. – 50 (33.3%) patients with grade 1 CCI; 2 gr. – 50 (33.3%) patients with grade 2 CCI; 3 gr. - 50 (33.3%) patients with grade 3 CCI. The control group consisted of 20 individuals with stage 1-2 CKD.

All 150 patients underwent all studies, including general clinical, biochemical, hormonal blood tests and the neuromarker BDNF in the blood, as well as instrumental studies.

Results and its discussion. In the control group, the average BDNF values were within 2.1 ± 0.23 ng/ml. Serum levels of BDNF in groups of patients with type 2 diabetes significantly decreased in comparison with the control group as the degree of CCI increased: in group 1 it was $0.8 \pm 0.04^{**}$, in group 2 $0.5 \pm 0.09^{**}$ and in group 3 $0.2 \pm 0.06^{**}$ ng/ml.

We have developed and proposed the degree of BDNF deficiency in the blood: mild deficiency with BDNF from 0.8 to 0.9 ng/ml, moderate deficiency with BDNF from 0.4 to 0.7 ng/ml and severe deficiency with BDNF from 0.2 to 0.3 ng/ml (control 2.1 ± 0.23 ng/ml).

Conclusions. Serum levels of BDNF in groups of patients with DM 2 and CKD on hemodialysis significantly decreased compared to the control group as the degree of CCI increased and can serve as a reliable prognostic criterion for the development of worsening cerebral deficits (stroke) in this cohort of patients.

Abstract-ID: 292

TO ASSESS THE STATUS OF NEUROPSYCHOLOGICAL STATUS (DEPRESSION, ANXIETY) DEPENDING ON THE FORM OF CUSHING'S SYNDROME

Shakhnoza Ergashova¹, Narimova Gulchekhra², Ogiljon Saitmuratova³

¹Republican Specialized Scientific Practical Medical Center of Endocrinology Named after Academician Y.K.Turakulov, Neuroendocrinology, Tashkent, Uzbekistan

²Republican Specialized Scientific Practical Medical Center of Endocrinology Named after Academician Y.K.Turakulov, Neuroendocrinology, Tashkent, Uzbekistan

³Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

The purpose of the work: To study neuropsychological status, including depression, anxiety in patients with CS depending on the duration of hypercortisolemia and disease activity

Research materials and methods: We analyzed the level of depression and anxiety in 200 patients with CS, who were examined and treated at the Republican Specialized Scientific and Practical Medical Center of Endocrinology (Tashkent). The average age of patients was 34.67 ± 0.64 years, while women - 150 (75%) and men - 50 (25%). The Hospital Anxiety and Depression Scale (HADS) was used to assess depression and anxiety. The CushinQoL questionnaire was used to assess the quality of life of patients

Study results: According to the etiological factor, patients were divided into two groups: ACTH-dependent CS in 170 (85%) patients (of which 143(71.5%) women and 27(13.5%) men) and ACTH-independent CS in 30 (15%) patients (of which 27 (13.5%) women and 3(1.5%) men). After the pathogenetic above methods of treatment, 32(64%) men achieved remission, 16 (32%) men did not achieve remission, and 2(4%) patients relapsed the disease. After treatment in women, remission was achieved in 97 (64.67%) cases, remission was not achieved in 35 (23.33%) patients, and the disease relapsed in 18(12%) patients. Prior to treatment, 170(85%) patients with ACTH with dependent CS were diagnosed with clinically pronounced depression ($14,04 \pm 0,23$ point) and subclinical pronounced anxiety ($8,11 \pm 0,29$ point), and QoL was $21,07 \pm 0,53$ point (35.12%). After treatment (after an average of $5,81 \pm 0,48$ years), subclinical severe depression ($9,29 \pm 0,29$ point) was determined, anxiety was determined and amounted to $4,46 \pm 0,27$ points, and QoL was $37,46 \pm 0,32$ points (62.43%). Prior to treatment, 30 (15%) patients with ACTH with independent CS were diagnosed with clinically pronounced anxiety ($13,32 \pm 0,48$ point) and subclinical pronounced depression ($8,81 \pm 0,71$ ball) and QoL was $22,24 \pm 0,81$ points (37.07%). After the treatment (after an average of $5,64 \pm 0,79$ years), anxiety and depression did not reveal (respectively $3,65 \pm 0,38$ a point and a $3,81 \pm 0,4$ point, $p < 0.001$ and QoL significantly improved to $53,66 \pm 0,68$ points (89.43%, $p < 0.001$).

Conclusions: The questionnaire in patients with CS revealed that clinical depression ($14,04 \pm 0,23$ point) was more pronounced in patients with ACTH dependent CS, and clinically severe depression ($13,32 \pm 0,48$ point) prevailed in patients with ACTH independent CS.

Abstract-ID: 293

“RESULTS OF SCREENING FOR CARBOHYDRATE METABOLISM DISORDERS IN THE KHOREZM REGION OF THE REPUBLIC OF UZBEKISTAN”

Gulchekhra Narimova¹, Gulrukh Kulimova²

¹*Republican Specialized Scientific Practical Medical Center of Endocrinology, Republican Specialized Scientific and Practical Medical Center of Endocrinology of the Ministry of Health of the Republic of Uzbekistan Named after Academician. Y.H. Turakulov, Thyroidology, Tashkent, Uzbekistan*

²*Khorezm Regional Endocrine Ambulance, Urgench, Uzbekistan*

Background. Despite numerous approaches, including lifestyle changes and pharmacological and non-pharmacological treatments, aimed at curbing the syndrome, the prevalence of obesity and type 2 diabetes mellitus (T2DM) has continued to rise worldwide, and no country has been able to reduce the prevalence of either of these diseases. Therefore, there is a need for a better understanding of the pathogenesis of complex disease and an improved understanding of modifiable risk factors to reduce the burden of obesity and T2DM.

Purpose of the study. To study the prevalence of some risk factors for T2DM mellitus in the Khorezm region according to screening data.

Material and research methods. The study was conducted in the Khorezm region during November 2020. In this region with a population of 1,893,059 people, only 1,829,610 individuals (96.6%) were covered.

The examined individuals were divided into the following groups according to the degree of risk of developing T2DM : group 1 - healthy individuals - 879,645 people (48.1%), group 2 - 407,759 individuals (22.4%) were low risk, group 3 - 473,759 individuals (25.9%) were in the medium-risk group and group 4 - 68,447 individuals (3.7%) were in the high-risk group.

Subsequently, the selected patients underwent anthropometric, biochemical, hormonal (insulin, C-peptide) blood tests, as well as ECG, chest x-ray and instrumental studies, as well as statistical techniques.

Research results. According to the results of registration of 1,829,610 individuals examined, 447,778 of them (24.5%) were found to be overweight, and 229,175 individuals (12.5%) were diagnosed with varying degrees of obesity.

It was found that 427,613 (35.5%) individuals had overweight, 185,301 (15.4%) had grade 1-2 obesity, and 39,830 (3.3%) of the population had grade 3 obesity.

Among the examined children, 20,165 (3.2%) were found to be overweight, and 4,044 children (0.6%) were found to have varying degrees of obesity.

Conclusions: Of the 1,829,610 individuals examined in the Khorezm region, 447,778 (24.5%) were found to be overweight, and 229,175 individuals (12.5%) were diagnosed with varying degrees of obesity, which indicates the need for further research in these risk groups.

Abstract-ID: 294

ASSESSMENT OF THE INDICATORS OF QUALITY OF LIFE, DEPRESSION AND ANXIETY IN PATIENTS WITH ACTH DEPENDENT CUSHING SYNDROME (IN REMISSION) DEPENDING ON THE DURATION OF HYPERCORTISOLISM

Shakhnoza Ergashova¹, Gulchekhra Narimova², Ogiljon Saitmuratova³

¹Republican Specialized Scientific Practical Medical Center of Endocrinology Named after Academician Y.K.Turakulov, Neuroendocrinology, Tashkent, Uzbekistan

²Republican Specialized Scientific Practical Medical Center of Endocrinology Named after Academician Y.K.Turakulov, Tashkent, Uzbekistan

³Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan

The clinical manifestations of Cushing syndrome (CS) vary, partly depending on the degree and duration of cortisol excess.

The purpose of the work: To study the indicators of quality of life, depression, anxiety in patients with CS depending on the duration of hypercortisolemia of the disease.

Research materials and methods: We analyzed the level of depression and anxiety in 100 patients with ACTH dependent in remission. The average age of patients was 34.67 ± 0.64 years, while women - 75 (75%) and men - 25 (25%). The Hospital Anxiety and Depression Scale (HADS) was used to assess depression and anxiety.

Results of studies: Analysis of QoL, anxiety and depression parameters in patients with ACTH dependent CS (in remission stage) was carried out depending on the duration of hypercortisolemia. The change in the QoL score in patients with hypercortisolemia duration up to 2 years (n=6), these indicators were (before treatment) $20,67 \pm 1,04$ points, $7,3 \pm 0,84$ points, $12 \pm 0,87$ points, respectively, and after treatment, when they achieved remission, QoL improved to $43 \pm 1,24$ points and the absence of symptoms of anxiety and depression was noted ($3,33 \pm 0,3$ points, $6,33 \pm 0,38$ points ($p < 0.001$)). QoL scores in pre-treatment patients with hypercortisolemia lasting 2-5 years (n=47) were $21,26 \pm 0,46$ points, $7,87 \pm 0,29$ points, $13,9 \pm 0,37$ points, respectively, and improved to $37,7 \pm 0,88$ points, with no symptoms of anxiety ($4,57 \pm 0,32$ points) and subclinical depression ($8,6 \pm 0,38$ points ($p < 0.001$)). Assessment of QoL in patients before treatment with hypercortisolemia lasting 5-10 years (n=39), these indicators were the following $20,38 \pm 0,38$ points, $8,33 \pm 0,41$ points, $15,1 \pm 0,32$ points, respectively, and after treatment there were improvements in QoL to $35,59 \pm 1,02$ points, no symptoms of anxiety ($4,92 \pm 0,3$ points) and clinically pronounced depression ($11,03 \pm 0,32$ points ($p < 0.001$)). Analysis of QoL scores in patients with hypercortisolemia for more than 10 years (n=8), these pre-treatment scores were $19,88 \pm 0,78$ points, $9,5 \pm 0,53$ points, $17,63 \pm 0,77$ points, respectively, and after treatment, there was an improvement in $33,63 \pm 1,12$ points, absence of anxiety symptoms ($5,88 \pm 0,34$ points), and clinically severe depression ($13,63 \pm 1,32$ points ($p < 0.01$)).

Conclusions: The activity of Cushing's syndrome affects the degree of quality of life, depression and anxiety, but subclinical depression ($10,5 \pm 0,3$, $p > 0.05$) was detected in patients with ACTH dependent CS in remission, even with improved quality of life. Prolonged hypercortisolemia in patients with CS causes poor quality life, symptoms of depression and anxiety of varying degrees.

Abstract-ID: 297

GROWTH AND FORMATION OF THE ADRENAL CORTEX IN OFFSPRING UNDER CONDITIONS OF PRENATAL EXPOSURE TO PESTICIDES THROUGH THE MOTHER'S BODY

Dilnoza Sabirova¹, Gulzoda Negmatova²

¹*Samarkand State Medical University, Department of Endocrinology, Samarkand, Uzbekistan*

²*Samarkand State Medical University, Samarkand State Medical University, Endocrinology, Samarkand, Uzbekistan*

Currently, in various countries of the world, research continues in the following priority areas of identifying the toxic effects of intrauterine and early postnatal exposure to pesticides, including: developing methods for preventing the endocrine-disrupting effect of pesticides in the postnatal period based on studying their mechanisms; to determine the concentration of marker hormones of the anterior pituitary gland, thyroid and adrenal glands; to substantiate the morphological mechanisms of the toxic effects of small doses of pesticides in early postnatal ontogenesis; to identify the state of cell proliferation and apoptosis processes in the organs and tissues of the offspring under exposure to pesticides through the mother's body.

Purpose of the study: Identification of the structural and functional features of the early postnatal formation of the adrenal cortex in the offspring of animals with chronic exposure to pesticides on the mother's body.

Materials and research methods: To study the morphology of cells of the adrenal cortex in 25 control animals and 45 experimental animals during different periods of pre- and postnatal ontogenesis, and conduct a comparative analysis with data from control animals.

Results: The study of the morphology and morphometric indicators of the structures and local regulatory apparatus of the adrenal cortex in offspring with prenatal exposure to pesticides through the mother's body makes it possible to determine the mechanisms of occurrence of congenital pathologies of the adrenal cortex and diseases developing as a result of these congenital pathologies.

Conclusion: Chronic exposure to small doses of pesticides on the maternal body during pregnancy and lactation leads to an "endocrine-disrupting" effect in the offspring in the early postnatal period.

Abstract-ID: 298

INCREASED RISK OF METABOLIC SYNDROME IN PATIENTS WITH VITILIGO

Umida Mirsaidova¹

¹*Republican Specialized Scientific and Practical Medical Center of Endocrinology Named after Academician E. H. Turakulov*

Background: Inflammatory and immune processes can be triggered in vitiligo due to a decreased number of melanocytes and their anti-inflammatory effects. Because of the systemic nature of vitiligo, metabolic abnormalities such as insulin resistance and lipid profile disturbances as well as skin involvement may be observed in vitiligo.

Aims: To investigate the association between metabolic syndrome and vitiligo.

Study Design: Case-control study.

Methods: The demographic, clinical and laboratory features in the subjects were compared according to presence of vitiligo and metabolic syndrome [patients (n=80) vs. gender-age matched controls (n=20) and metabolic syndrome positive (n=68) vs. negative (n=15)]. A logistic regression analysis was also used.

Results: We identified metabolic syndrome in 68(85.0%) subjects with vitiligo and 15 (15.0%) subjects without vitiligo (p=0.04). Active vitiligo, segmental vitiligo, an increased duration of vitiligo and an increased percentage in the affected body surface area were determined to be independent predictors of metabolic syndrome [activity of vitiligo: p=0.012, OR (95% CI)=64.4 (2.5-1672); type of vitiligo: p=0.007, OR (95% CI)=215.1 (4.3-10725.8); duration of vitiligo: p=0.03, OR (95% CI)=1.4 (1.1-2.0); percentage of affected body surface area: p=0.07, OR (95% CI)=1.2 (0.98-1.5)].

Conclusion: The risk of developing metabolic syndrome is increased in patients with vitiligo. The poor clinical features of vitiligo, such as active, extended and segmental vitiligo with an increased duration of time, are independent predictors for developing metabolic syndrome.

Keywords: Metabolic syndrome, vitiligo, screening Vitiligo

Abstract-ID: 299

MALIGNANT PROLACTINOMA: A RARE AND CHALLENGING CLINICAL ENTITY

Inês Manique¹, Sara Amaral¹, Teresa Rego², Ana Palha¹, Luísa Cortez¹, Amets Sagarrabay³, Luís Cerqueira⁴, Carlos Pontinha⁵, José Silva-Nunes¹

¹*Centro Hospitalar Universitário Lisboa Central, Endocrinology, Diabetes and Metabolism, Lisboa, Portugal*

²*Hospital de Santo Espírito Da Ilha Terceira, Endocrinology, Angra Do Heroísmo, Portugal*

³*Centro Hospitalar Universitário Lisboa Central, Neurosurgery, Portugal*

⁴*Centro Hospitalar Universitário Lisboa Central, Neuroradiology, Lisboa, Portugal*

⁵*Centro Hospitalar Universitário Lisboa Central, Anatomic Pathology, Lisboa, Portugal*

Background: Malignant prolactinomas are very rare and defined by the presence of cerebrospinal, meningeal or distant metastasis. Diagnostic and therapeutic approaches are challenging since sustained response to treatment is usually bad.

Case Report: 52 year-old male, was diagnosed in January 2019 with a macroprolactinoma (MRI: anteroposterior 27mm x transversal 29 mm x vertical 25 mm, with supra and infrasellar growth and right cavernous sinus invasion) (Prolactin 470 ng/mL, reference 4,04-15,2). Despite increasing cabergolin dose for 2 years (until 3 mg/week), prolactin level did not get normal (2904,56 ng/mL; reference 3,46-19,4) and MRI described an increased predominantly solid sellar lesion with 29x32x30 mm molding the optic chiasm, with sphenoidal sinus and bilateral cavernous sinus invasion (Knosp 4). Clinically, compressive symptoms got worse with appearance of diplopia and ptosis (sixth cranial nerve palsy) and hypopituitarism. He underwent neurosurgery intervention in February 2021 (Pathology: solid prolactinoma, Ki67/mib1 20-30%; 2 mitosis/10 HPF). After that, he maintained hyperprolactinemia (208,94 ng/mL) and hypopituitarism. Five months later, headaches started again with trigeminal neuralgia and left eye ophthalmoplegia. Prolactin increased until 2685 ng/mL, under cabergolin 3 mg/week. MRI revealed a residual/recurrent lesion (26x26x22 mm) with increased left cavernous sinus invasion. After surgical reintervention in July 2021 (pathology: prolactinoma; Ki67/mib1 25%; 5/10 mitosis/HPF), stereotaxic radiotherapy was performed (54 Gy in 30 fractions). Six months later, clinically better, prolactin was 41,9 ng/mL under 2 mg/week; MRI revealed a little residual tumor in the left cavernous sinus. One year later, prolactin and the residual tumor increased progressively. During investigation for an intense and limiting left back pain, a CT revealed suspicious 2 juxtapleural lung lesions; an heterogeneous and lobulated abdominal mass (78x57,5 mm) between left flank and left iliac fossa, in relation with left retus muscle and ileal loops; and osteolytic mass in S1-S2 vertebrae with intracanalicular invasion. The biopsy of the intra-abdominal mass revealed a prolactinoma metastasis (Ki67/mib1 40-50%). At that time, prolactin was 4700 ng/mL under 4 mg/week of cabergolin and residual prolactinoma presented 15,5 mm. The patient was then referred to Oncology Department with intention to start chemotherapy and perform palliative sacral radiotherapy.

Conclusion: We report a very rare clinical report of a malignant prolactinoma with confirmed abdominal and possibly thoracic and sacral metastasis. In this case, the presence of a resistant prolactinoma with an aggressive biological behavior (high Ki67), even after the referred treatment (medical, surgical and stereotaxic radiotherapy), increased the clinical suspicion for malignant prolactinoma. However, clinical, pathological and molecular predictors of malignant prolactinomas remain to be clearly understood.

Abstract-ID: 300

VITILIGO AND METABOLIC SYNDROME: SYSTEMATIC REVIEW

Umida Mirsaidova¹

¹*Republican Specialized Scientific and Practical Medical Center of Endocrinology Named after Academician E. H. Turakulov*

Background: Metabolic syndrome (MetS) has been associated with various skin conditions including vitiligo. However, the association between these 2 conditions has yet to be determined by quantitative meta-analysis.

Objective: The aim of this paper was to determine the association between vitiligo and metabolic syndrome via systematic review and meta-analysis.

Methods: A systematic literature search of Pubmed, Embase, Cochrane, and Web of Science was performed for all published literature prior to August 16, 2020. Case control and prospective cross-sectional studies analyzing the association between vitiligo and MetS were included in this review. The primary outcome measures include the type of vitiligo, diagnostic criteria for MetS, components of MetS (waist circumference, blood pressure, triglycerides, fasting glycemic index, and high-density lipoprotein cholesterol), low-density lipoprotein cholesterol levels, and BMI. A meta-analysis was performed to evaluate the prevalence and association of MetS in patients with vitiligo.

Results: A total of 6 studies (n=734 participants) meeting eligibility criteria were included for systematic review and meta-analysis. The pooled prevalence of MetS in patients with vitiligo was (0.296, 95% CI 0.206, 0.386; $P<.001$). Patients with vitiligo were no more likely to develop MetS compared to control patients (odds ratio 1.66, 95% CI 0.83, 3.33; $P=.01$). A leave-one-out sensitivity analysis showed a significant association between MetS and vitiligo ($P<.001$). Significant elevations in fasting glycemic index (mean difference 5.35, 95% CI 2.77, 7.93; $P<.001$) and diastolic blood pressure (mean difference 1.97, 95% CI 0.02, 3.92; $P=.05$) were observed in patients with vitiligo compared to control patients.

Conclusions: The association between vitiligo and metabolic syndrome carries important clinical implications. Dermatologists and other multidisciplinary team members should remain vigilant when treating this patient population in order to prevent serious cardiovascular complications that may arise as a result of metabolic disease.

Abstract-ID: 301

OPHTHALMIC ASPECTS OF THE “EMPTY” TURKISH SADDLE SYNDROME

Dildora Abidova¹

¹*Republican Specialized Scientific and Practical Center Named after Academician Ya.H. Turakulov, Tashkent, Uzbekistan*

The aim of the study is neuro-ophthalmologic aspects of the syndrome of primary “Empty” Turkish saddle syndrome.

Material and methods. A total of 25 patients (19 women and 6 men) with the syndrome of primary “empty Turkish saddle” aged 24-55. Lack of diaphragm sella (according to MRI) has been diagnosed in all cases. Among the etiologic factors affecting the development of the “empty Turkish saddle” according to the results of MRI the increased intracranial pressure in 21 patients and the presence of benign intracranial hypertension in 7 patients could be also noted. Patients addressed to the Republican Specialized Scientific and Practical Center named after Academician Ya.H. Turakulov with complaints of visual disturbances (in a period of 3 weeks to 0.5-1.0 years from onset). In addition, in almost all cases, the patients complained of almost constant headache of varying degrees with no specific localization, rise in blood pressure, heart pain, shortness of breath caused by increased intracranial pressure and autonomic disturbances. Ophthalmologic examination included visometry, refractometry, tonography, automated static perimetry, and oftalmo-biomicrometry.

While examining the papilledema of varying severity in 10 patients, 2 patients with secondary atrophy of the optic nerve, in 1 case the thrombosis of the central retinal vein. Change in the field of view was diagnosed in 13 patients: in 5 –concentric constriction of varying severity, in 4 – incomplete bitemporal hemianopsia, in 3 – central and paracentral scotoma and in 1 case – binasal hemianopsia.

Results. The syndrome of primary “empty Turkish saddle” syndrome is a syndrome, which is based on the endocrine, neurological and visual disturbances. The etiology and pathogenesis of congenital deficiency syndrome define diaphragm sella and intracranial hypertension. In the basis of the above-mentioned neuro-oftalmic changes there are an intracranial hypertension and hemodynamic abnormalities in the basin of the internal carotid and orbital arteries.

Conclusion. The research of the ophthalmic manifestations of the “empty” Turkish saddle syndrome arise big interest for the ophthalmologists in cases of the visual impairment which are not caused by ophthalmic pathology.

Abstract-ID: 302

THE ROLE OF MMP-1 AND FGFR4-R388 GENE POLYMORPHISMS IN PITUITARY ADENOMA

Mijgona Safarova¹

¹*Republican Specialized Scientific and Practical Center Named after Academician Ya.H. Turakulov, Tashkent, Uzbekistan*

Background. The pathogenesis of pituitary adenoma (PA) is complex and poorly understood. It is thought that PA has a multifactorial aetiology; genetic factors also have an impact on PA development. Since *MMP1* and *FGFR4* genes play an important role in tumour growth, differentiation and progression, we decided to determine if the frequency of the genotypes of *MMP-1* and *FGFR4-R388* polymorphisms influence the development of PA.

Materials and methods. The study enrolled $n = 321$ patients with PA and $n = 20$ healthy controls (reference group). The genotyping tests of *MMP-1* and *FGFR4-R388* were carried out using the real-time polymerase chain reaction (PCR) method.

Results. The polymorphism in the *MMP-1* gene 1G/1G genotype was more frequent in the group of invasive PA than in the control group: 28.6% vs. 16.5%, $p = 0.044$. The 1G/2G genotype was more frequent in females of the control group compared to PA group females: 50.3% vs. 30.8%, $p = 0.011$. The polymorphism in the *MMP-1* gene 1G/1G genotype was more frequent in the active PA group than in the control group: 28.4% vs. 16.5%, $p = 0.044$. *FGFR4-R388* did not play any predominant role in PA development.

Conclusion. The *MMP-1* gene 1G/1G may play a role in invasive and active PA development.

Keywords: pituitary adenoma, matrix metalloproteinase-1, FGFR4-R388, gene polymorphism

Abstract-ID: 303

PREVALENCE OF METABOLIC SYNDROME AND PREDICTORS FOR THE DEVELOPMENT OF METABOLIC SYNDROME IN PATIENTS WITH ACROMEGALY: A RETROSPECTIVE, NON-INTERVENTIONAL, BICENTRIC COHORT STUDY

Xenia Xipp¹, Matthias Auer², Günter Stalla³, Anastasia Athanasoulia-Kaspar⁴

¹Klinik für Anaesthesiologie am Klinikum Rechts der Isar, Ismaninger Str. 22, 81675 Munich

²Medizinische Klinik und Poliklinik IV, Klinikum der Universität München (Lmu), Medizinische Klinik IV, Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, LMU München, Munich, Germany, München, Germany

³Medicover Neuroendokrinologie Mvz, Med. Klinik und Poliklinik Iv; Ludwig-Maximilians-Universität Münc, Munich, Germany, Endokrinologie, München, Germany

⁴Medicover Neuroendokrinologie Mvz, Orleansplatz 3, 81667, Munich, Medizinische Klinik und Poliklinik IV, LMU, Ziemssenstraße 5, 80336 Munich, Praxis für Neuroendokrinologie Prof. Stalla und Kollegen, München, Germany

Aim: The aim of this study is to evaluate the prevalence of changes in terms of metabolic syndrome (MetS) and to identify predictors for the development of MetS in patients with acromegaly.

Background: Although individual metabolic risk factors such as dyslipidemia, insulin resistance or diabetes mellitus and arterial hypertension are well documented in acromegaly patients, studies specifically investigating the MetS as entity in these patients' group are lacking.

Methods: In this retrospective cohort study, we compared acromegaly-specific, clinical and MetS parameters among 88 acromegaly patients from the Neuroendocrine Department of the Max Planck Institute of Psychiatry and the Medizinische Klinik und Poliklinik IV of the Ludwig Maximilian University of Munich before and after therapy, both medical and surgical. Patients were evaluated before and at least 6 months after treatment and were categorized to be controlled or not. Prevalence of MetS was evaluated by the criteria of the International Diabetes Federation (2006). As possible predictors for MetS gender, age ≥ 50 years, disease duration, pituitary insufficiency, biochemical control and medical treatment of acromegaly were examined.

Results: The prevalence of MetS did not significantly change before and after treatment (35,0 % vs. 39,3 %). During treatment GH, IGF-1, diastolic blood pressure (DBP), basal insulin and HOMA index decreased considering all study participants, whereas HDL cholesterol (HDL-C) increased. Even within the biochemically uncontrolled cohort the same changes were observed apart from a decrease in DBP. The biochemically controlled cohort showed decreased DBP and increased HDL-C. Additionally, these patients showed an increasing, yet not significant, trend in body weight and BMI. Biochemically controlled patients also showed elevated waist circumference compared to uncontrolled patients. Age ≥ 50 years within the controlled patients was associated with a higher risk of MetS, elevated glucose parameters and high blood pressure. Pituitary insufficiency was somehow protective for developing high blood pressure, whereas male patients were protected from arterial hypertension.

Conclusion: The central findings of this study are that treatment of acromegaly can partially revise changes in parameters of MetS. With respect to most metabolic changes, the decrease of GH and IGF-1 levels by initiating therapy seems to be crucial but not the achievement of biochemical control. However, biochemical control seems to have unfavorable effects on patients' body composition. This group of patients might have a higher risk of developing MetS and therefore should be particularly well screened for MetS to receive earlier treatment.

Friday, December 08th, 2023

Poster Presentations

Abstract-ID: 21**INACTIVE PITUITARY ADENOMAS: VISUALIZATION FEATURES**Dilorom Kholova¹, Zamira Khalimova²¹Republican Specialized Scientific Practical Medical Center of Endocrinology, Republican Center of Endocrinology, Tashkent, Uzbekistan²Republican Specialized Scientific-Practical Medical Center of Endocrinology, Republican Center of Endocrinology, Republican Center of Endocrinology, Tashkent, Uzbekistan

Target. For modern endocrinology, the question of early diagnosis of formations of the hypothalamic-pituitary region is important, since even highly informative computed tomography (CT) and magnetic resonance imaging (MRI), as well as clinical laboratory, enzyme immunoassay, hormonal studies do not give the correct answer up to 30 - 55 % of cases, and with microadenomas (tumor sizes up to 10 mm) 80-90% of cases. Based on the above, the purpose of this study was to study the structure of inactive pituitary adenomas in MRI studies in patients with a verified diagnosis.

Material and methods. The study included 325 patients with inactive pituitary adenoma (145 women and 180 men aged 18 to 70 years (44.5±3.85 years). Mean age 15-70 (43.6±3.84) years. Disease duration from the moment of diagnosis based on anamnesis and MRI studies from 1 to 15 years.

Results and discussion. The studied patients had adenomas with intrasellar -74, parasellar - 41, infrasellar - 23, infraparasellar - 26, suprasellar - 14, supraparasellar - 25, suprainfrasellar - 13, suprainfraparasellar - 12, suprainfraparasellar - 97.

In MRI study, the structure of pituitary adenomas was predominantly solid (n=269) and cystic (n=31). In 25 cases, the structure of pituitary adenomas was represented by a hemorrhagic component, and in 32 of them both cystic and hemorrhagic components were present.

In 271 cases, the tumor structure was relatively homogeneous, in 54 - heterogeneous. MRI images of 54 patients with IPA had hypointense on T1 and isointense on T2-weighted images, 204 cases were hypointense on both T1- and T2-weighted images, 28 tumors were hypointense on T1-weighted images and hyperintense on T2-weighted images. weighted images, 11 cases were isointense on T1-weighted images and hypointense on T2-weighted images, and 9 cases were isointense on T1-weighted images and hyperintense on T2-weighted images.

Conclusion. Thus, during MRI examination, the majority of inactive pituitary adenomas had intrasellar (29.8%) and suprainfraretrosellar (19.7%) distribution, in 82.8% of cases they had a solid structure, in 7.7% of cases they contained cystic inclusions, in 9.5% - hemorrhagic component. The MR signal from the adenoma tissue is predominantly hypointense, both on T2-weighted images (66.2%) and T1-weighted images (88.0%). The provisional diagnosis of "Inactive pituitary adenoma", established on the basis of clinical, hormonal and neuroimaging examination of patients, may not be confirmed by morphological examination of the removed tumor tissue, which suggests that the clinical term "inactive pituitary adenoma" may include various nosological units and only morphological studies can currently be the only reliable criterion in confirming the diagnosis of inactive pituitary adenoma.

Abstract-ID: 22**SURGERY FOR INACTIVE PITUITARY ADENOMAS**Dilorom Kholova¹, Zamira Khalimova²¹Republican Specialized Scientific Practical Medical Center of Endocrinology, Republican Center of Endocrinology, Tashkent, Uzbekistan²Republican Specialized Scientific-Practical Medical Center of Endocrinology, Republican Center of Endocrinology, Republican Center of Endocrinology, Tashkent, Uzbekistan

Target. Dynamic assessment of visual functions, symptoms of pituitary insufficiency and study of the frequency of relapses of inactive pituitary adenomas (IPA), taking into account general clinical, ophthalmological, imaging, and hormonal parameters in patients with a verified diagnosis who applied to the RSSPMS of Endocrinology after transsphenoidal transnasal adenomectomy.

Material and methods. In the period from 2018 to 2022, 427 patients with various pituitary adenomas were operated on at the Neurosurgery Department of the RSSPMS of Endocrinology TAG. 188 case histories of patients with IPA operated from 2018 to 2022 were retrospectively analyzed. Follow-up of patients after the first operation ranged from 1 to 3 years. Of the 188 patients, 32.4% (n=61) were men and 67.6% (n=127) were women. 151 patients had a macroadenoma (up to 40 mm), the rest - 37 - giant tumor sizes (any size over 40 mm).

Results. The main complaints in patients before surgical treatment were a decrease in visual acuity - in 68.8% of patients, in patients of reproductive age (men under 55 years of age and women under 50 years of age) - sexual dysfunction (81% and 83%, respectively), headaches (100%). Chiasmal syndrome in the form of optic nerve atrophy of varying degrees and bitemporal hemianopsia or hypopsia was observed in 133 (70.7%) patients. Insufficiency of one or more functions of the pituitary gland in varying degrees of severity was diagnosed in 100% of patients, including secondary hypothyroidism in 18 patients (9.6%) - 3 men and 15 women, secondary hypothyroidism with hypogonadism - in 86 (45.9%) patients - 33 men and 53 women, secondary hypothyroidism with secondary hypocorticism in 34 (18.1%) patients - 11 men and 23 women, secondary hypogonadism with secondary hypocorticism - in 37 (19.7%) patients - 10 men and 27 women and 13 (6.7%) patients (4:9) had symptoms of panhypopituitarism. In our series of patients, tumor recurrence was found in 32 (17.0%) operated patients (23 women and 9 men), whose cytological analysis of the removed adenoma showed a null-cell tumor. Signs of recurrence of the disease were a decrease in visual acuity - in 6 patients, in 19 women menstrual irregularities, in 7 women relapse was detected as a result of systematic control MRI studies and all patients had persistent headaches pain.

Conclusion. After surgical treatment, it is necessary to control the level of tropic hormones of the pituitary gland, the level of PRL and hormones of peripheral endocrine glands, as well as urine analysis according to Zimnitsky for the diagnosis of diabetes insipidus.

Abstract-ID: 44**PITUITARY APOPLEXY AFTER INITIATION OF TRIPTORELIN THERAPY IN A PROSTATE CANCER PATIENT – CASE REPORT AND LITERATURE REVIEW**

Naomi Even-Zohar (MD, PhD)¹, Sapir Anani (MD)¹, Elad Shemesh (MD)¹, Merav Serebro (MD)¹, Esther Osher (MD, PhD)^{1,2}, Yona Greenman (MD)^{1,2}.

¹Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

²Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Pituitary apoplexy (PA) is an uncommon clinical syndrome characterized by the infarction or hemorrhage of the pituitary gland, typically occurring in a pre-existing pituitary adenoma. The use of gonadotropin-releasing hormone agonists in the context of stimulation tests or therapy is one of the various predisposing factors associated with PA.

Case presentation: A 73-year-old patient with an underlying diagnosis of prostate cancer presented to the emergency room with fever, impaired consciousness, and blurry vision. Upon arrival, he was started on parenteral antibiotic treatment for suspected pneumonia, and a brain MRI was performed due to his neurologic symptoms, including bitemporal hemianopsia in the visual field test. The MRI revealed a sellar and suprasellar lesion exerting pressure on the optic chiasm and displaying heterogeneous contrast enhancement suggestive of recent hemorrhage. A revision of the F-18 choline PET CT scan performed a few months earlier confirmed the previous existence of a pituitary macroadenoma. Subsequent inquiry revealed that the patient had received the first dose of Triptorelin just hours before presenting to the emergency room as part of his prostate cancer treatment. Laboratory assessments revealed panhypopituitarism. The patient was started on appropriate replacement therapy and referred for transsphenoidal surgery. Pathological examination confirmed the presence of an apoplectic pituitary adenoma, with positive staining for SF-1, consistent with the gonadotroph lineage. The patient developed mild DI following the surgery, and daily desmopressin was added to his treatment. There was an improvement in the patient's visual fields. A thorough review of the existing literature unveiled 31 reported cases in which GnRH analogs were associated with the occurrence of pituitary apoplexy. Twenty-four of those were in the context of prostate cancer treatment, three were following dynamic tests, and other rare causes were breast cancer treatment, severe menorrhagia, and assisted reproduction therapy. Pituitary apoplexy as a complication of GnRH analog administration is rare, underscoring the importance of maintaining a high level of suspicion for early diagnosis and intervention.

Abstract-ID: 62

CLINICAL AND SOCIO-DEMOGRAPHIC CHARACTERISTICS OF A COHORT OF ADULTS IN TREATMENT WITH A BIOSIMILAR HUMAN GROWTH HORMONE IN OUR PITUITARY UNIT

Andres Jimenez Sanchez¹, Eva Maria VENEGAS MORENO¹, Pablo Jesús Remón Ruiz¹, María Elena Dios Fuentes¹, Jaime Perea Cortés², Bothayna Oulad Ahmed³, ALFONSO SOTO¹

¹Instituto de Biomedicina de Sevilla, Unidad de Endocrinología, Hospital Virgen del Rocío, Unidad de Gestión Clínica de Endocrinología Y Nutrición, Sevilla, Spain

²Instituto de Biomedicina de Sevilla, Unidad de Gestión Clínica de Endocrinología Y Nutrición, Sevilla, Spain

³Unidad de Endocrinología, Hospital Virgen del Rocío, Unidad de Gestión Clínica de Endocrinología Y Nutrición, Sevilla, Spain

MATERIALS & METHODS:

- Transversal study. •
- Variables: retrospectively collected from the digital health record of the Virgen del Rocío University Hospital, August 2023. •
- Numerical variables expressed as mean (standard deviation). Statistical significance: p-value < 0.05. •
- Elders: those ≥ 65 years old. •
- Quality of life: assessed with the Quality of Life-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) questionnaire. •
- IGF-1 reference values from our hormone laboratory are the following: •

Age	IGF-1 (ng/mL)
19 to 20 years	127 to 483
21 to 25 years	116 to 358
26 to 40 years	109 to 329
41 to 55 years	87 to 267
> 55 years	55 to 225

RESULTS:

- 53 patients under treatment, 7 elders. •
- 49.35 (19.68) years old •
- 22 (41.51%) men, 31 (58.49%) women. •

Etiology of the GH deficit	n
Congenital	9
Agenesis of the corpus callosum	1
Fetal hypoxia	1
Septo-optic dysplasia	1
Pituitary hypoplasia	5
Stratton-Parker syndrome	1
Idiopathic	6
Immune-mediated	3
Autoimmune hypophysitis	1
Histiocytosis	2
Traumatic brain injury	9
Tumoral	26
Acromegaly	1
Silent corticotropinoma	1
Unspecified pituitary adenoma	1
Craniopharyngioma	7
Cushing disease (corticotropinoma)	9
Dysgerminoma	2
Non-functioning pituitary adenoma	2
Prolactinoma	2
Rathke's cleft cyst	1

- Dosing:**
 - Treatment days per week: 6.37 (1.18). -
 - Dose per day: 0.342 (0.199) mg/day. -
 - Dose per kg and day: 0.004 (0.003) mg/kg/day. -

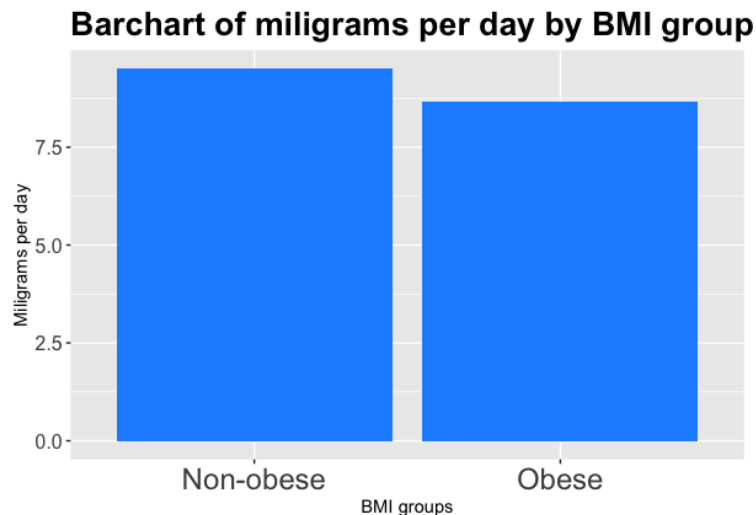
- Lipid panel:**
 - Total cholesterol 194.79 (32.25) mg/dL. -
 - HDL-cholesterol 57.5 (17.1) mg/dL. -
 - Triglycerides 131.5 (77.1) mg/dL. -

- Basic anthropometry:**
 - Height 1.659 (0.102) m. -
 - Weight 83.85 (18.41) kg. -
 - BMI 30.55 (6.76) kg/m². BMI in elders: 30.65 kg/m² vs young adults: 29.91 kg/m² (*p-value*=0.732). -
 - Waist-hip ratio 0.906 (0.111). Correlation with IGF-1: 0.052 (*p-value*=0.706). -

IGF-1: 142.73 (50.77) pg/mL. 7 (13.2%) patients were underdosed, all of which were elders. •

- Quality of life (QoL):**
 - 9.9 (8,4) points. -
 - QoL in men: 6 (15), women 12 (13) points (*p-value*=0.196). -
 - QoL in elders: 10.333, young adults: 7.285 (*p-value*=0.298). -
 - Correlation with IGF-1: -0.035 (*p-value*=0.800). -
 - Correlation with mg per day: -0.248 (*p-value* = 0.075) and per kg: -0.206 (*p-value*=0.155). -

- DEXA:**
 - Femoral neck bone mineral density (BMD): -1.16 (0.89) SDs. Correlation with IGF-1: 0.107 (*p-value*=0.600). -
 - DEXA total lumbar spine BMD: -0.88 (1.27) SDs. Correlation with IGF-1: -0.151 (*p-value*=0.449). -



CONCLUSIONS:

- Pituitary tumors were the first indication for growth hormone in adults, followed by traumatic brain injury. •
- A minority of patients were elders. •
- IGF-1 levels were not correlated with neither quality of life, bone mineral density nor waist-to-hip ratio. •

Abstract-ID: 63

OTHER HORMONE DEFICIENCIES AND SIDE EFFECTS IN A COHORT OF ADULTS IN TREATMENT WITH A BIOSIMILAR HUMAN GROWTH HORMONE IN OUR PITUITARY UNIT

Eva Maria VENEGAS MORENO¹, Andres Jimenez Sanchez¹, María Elena Dios Fuentes¹, Pablo Jesús Remón Ruiz¹, Jaime Perea Cortes², Bothayna Oulad Ahmed³, ALFONSO SOTO¹

¹Instituto de Biomedicina de Sevilla, Unidad de Endocrinología, Hospital Virgen del Rocio, Unidad de Gestión Clínica de Endocrinología Y Nutrición, Sevilla, Spain

²Instituto de Biomedicina de Sevilla, Unidad de Gestión Clínica de Endocrinología Y Nutrición, Sevilla, Spain

³Unidad de Endocrinología, Hospital Virgen del Rocio, Unidad de Gestión Clínica de Endocrinología Y Nutrición, Sevilla, Spain

MATERIALS & METHODS

- Variables: retrospectively collected from the digital health record of the Virgen del Rocío University Hospital, August 2023.
- Numerical variables expressed as mean (standard deviation). Statistical significance: p-value < 0.05.
- Elders: those ≥ 65 years old.
- Quality of life: assessed with the Quality of Life-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) questionnaire.
- IGF-1 reference values from our hormone laboratory:

Age	IGF-1 (ng/mL)
19 to 20 years	127 to 483
21 to 25 years	116 to 358
26 to 40 years	109 to 329
41 to 55 years	87 to 267
> 55 years	55 to 225

RESULTS

- 53 patients under treatment, 7 elders.
- 49.35 (19.68) years old.
- 22 (41.51%) men, 31 (58.49%) women.
- 51 patients had hormonal deficits:
 - 43 (81.13%) LH/FSH. -
 - 39 (73.58%) TSH. -
 - 37 (69.81%) ACTH. -
 - 10 (18.87%) AVP. -
- Pituitary tumors were the most frequent etiology of TSH deficit (24 cases, p-value = 0.035), ACTH (23, p-value = 0.043), FSH/LH (23, p-value = 0.042) and AVP (9, p-value = 0.037).
- 16.18 (5.39) years in treatment.
- 2 incident side effects (3.77%): 1 headache (continued), 1 dizziness (discontinued).
- 12 incident benign tumors during treatment in 10 patients.

Type	n
Colorectal microadenoma with low grade dysplasia	2
Congenital melanocytic nevus	2
Angiolipoma	1
Endometrial polyps	1
Fibrolipoma	1
Melanocytic nevus	1
Osteochondroma	1
Ovarian serous cystadenoma	1
Renal angiomyolipoma	1
Vulvar lipoma	1

3 incident benign tumors before treatment in 3 patients. •

Type	n
Lip leukoplakia	1
Nasal angiofibroma	1
Rectal ganglioneuroma	1

4 incident neoplasms during treatment in 4 patients. •

Type	n
Cutaneous basal cell carcinoma	2
Lymphomatoid papulosis	1
Squamous cell carcinoma	1

Incident neoplasms before treatment: 0. •

IGF-1 levels during treatment if: •

No tumor or neoplasms: 143.80 (53.75) ng/mL .a

Tumor: 144.00 (40.83) ng/mL .b

Neoplasm: 129.25 (49.28) ng/mL .c

In ANOVA analysis, we found no differences between groups regarding the variable "tumor" concerning IGF-1 ($p\text{-value}=0.863$) or age ($p\text{-value}=0.813$). •

Age at the first tumor: 38.73 (17.98) years, at 9.93 (13.22) years under treatment. •

CONCLUSIONS

Pituitary tumors had the most co-secretory deficits. •

A very low proportion of the sample developed side effects due to a biosimilar GH. •

The number of neoplasms under treatment was low and comprised by skin cancers. •

The development of tumors and neoplasms under treatment was not related to IGF-1 levels. •

Abstract-ID: 73

DETERMINATION OF CUSHING'S SYNDROME CHRONOTYPE WITH THE MUNICH CHRONOTYPE QUESTIONNAIRE AND ACTIGRAPHY

Mina Mazari¹, Stefanie Zopp¹, Nicole Reisch¹, Martin Reincke¹, Martha Merrow², Marily Theodoropoulou¹, Adriana Albani¹

¹ *Medizinische Klinik und Poliklinik IV, LMU Munich, Germany*

² *Institute of Medical Psychology, LMU Munich, Germany*

Chronotype refers to individual sleep timing within the 24-hour day. In humans, cortisol levels rise prior to waking, remain high through the day and are low during sleep. Patients with Cushing's syndrome, that have disrupted daily cortisol rhythms, report poor perceived quality of sleep.

We have previously initiated a prospective study to study the chronotype of patients with Cushing's syndrome and gathered evidence that it is significantly altered during active disease state, but comparable to control population during remission. Herein, we report data on 22 patients with active Cushing's syndrome and 66 patients in remission (36 of which under glucocorticoid substitution), compared to 38 control subjects.

Chronotype was determined with the Munich ChronoType Questionnaire (MCTQ) that assesses reported sleep-wake times and was analysed for mid sleep time on free days with a correction for sleep debt on workdays (MSFsc); data were matched for age. In addition, we gave actigraph devices (MotionWatch 8 by Camntech) to 10 patients with active Cushing's syndrome, 12 in remission and 13 control subjects for at least 13 days in order to monitor rest/activity cycles in an objective manner.

Patients with active Cushing's syndrome continued to present with a significantly earlier chronotype, as determined by MCTQ data (matched for age) compared to control subjects ($P < 0.001$) and patients in remission ($P = 0.009$). They showed significantly shorter sleep duration on workdays ($P = 0.016$ vs. control and $P = 0.02$ vs. remission) and work-free days ($P = 0.025$ vs. control and $P = 0.005$ vs. remission). Similarly, weekly sleep duration was significantly shorter only vs. remission ($P = 0.014$) but not vs. controls ($P = 0.87$).

They showed earlier sleep offset on workdays ($P < 0.001$ vs control) and ($P = 0.15$ vs. remission) but not on work-free days ($P = 0.258$ vs. controls) and ($P = 0.374$ vs. remission) and they had significantly earlier mid-sleep times (MSF) ($P = 0.041$) compared to control; but not to remission patients ($P = 0.138$). Sleep onset on free days was significantly earlier in Cushing patients vs. controls ($P = 0.002$) and vs. remission ($P = 0.04$).

Patients in remission also had significantly earlier sleep offset on workdays ($P = 0.038$) compared to control, but not on work-free days ($P = 0.892$). No differences were recorded for MSFsc ($P = 0.147$), MSF ($P = 0.634$), sleep onset on free days ($P = 0.108$), sleep duration during workdays ($P = 0.502$), and sleep duration during work-free days ($P = 0.924$).

Glucocorticoid substitution in remission patients did not affect their chronotype ($P = 0.576$).

Actigraphy data corroborated the MCTQ outcome: patients with active Cushing had significantly earlier chronotype (MSFsc) ($P = 0.002$ vs. control but not vs. remission ($P = 0.152$), earlier MSF compared to control ($P < 0.001$), but not to remission ($P = 0.128$). They also had significantly earlier sleep onset on workdays ($P = 0.044$).

The acrophase on free days measured by actigraphy also showed an earlier acrophase in patients with active Cushing compared to controls ($P = 0.004$). Patients in remission continued having earlier MSF compared to control ($P = 0.036$). In contrast, no significant differences were found between patients in remission and control in MSFsc ($P = 0.181$).

Finally, there was no significant difference between all groups concerning sleep duration on workdays and work-free days, weekly sleep duration, sleep offset on week and free days, sleep onset on free days, acrophase on weekdays as well as rho-, alpha- and total counts on week and free days.

Our data corroborate previous observations that endogenous hypercortisolism leads to an earlier chronotype that recovers, at least in part, after remission. Regularly filling the MCTQ could become a valid instrument in the diagnosis and follow-up of patients with Cushing's syndrome

Abstract-ID: 92

SAFETY OF GROWTH HORMONE REPLACEMENT (GHR) IN TUMOR-RELATED CHILDHOOD ONSET GROWTH HORMONE DEFICIENCY (CO-GHD) DURING TRANSITION TO ADULTHOOD

Mirjana Doknic¹, Marko Stojanovic², Tatjana Milenkovic³, Vera Zdravkovic⁴, Maja Jesic⁵, Slađana Todorovic⁶, Katarina Mitrovic⁷, Rade Vukovic⁸, Mihailo Milicevic⁹, Aleksandar Miodrag Stanimirović¹⁰, Mihajlo Curcic¹¹, Sandra Pekic Djurdjevic¹², Dragana Miljic¹³, Emilija Manojlović Gačić¹⁴, Ivana Cekic¹⁵, Ivan Jevtic¹⁶, Danica Grujicic¹⁷, Ivan Soldatovic¹⁸, Milan Petakov¹⁹

¹Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia, Medical Faculty, University Belgrade, Endocrinology, Belgrade, Serbia; ²Clinic for Endocrinology, Clinical Centre of Serbia, University of Belgrade, Belgrade, Serbia; ³Mother and Child Health Care Institute of Serbia "dr Vukan Cupic", Serbia; ⁴University Children's Clinic Tirsova, Medical Faculty, University Belgrade, Serbia; ⁵University Children's Clinic Tirsova, Medical Faculty, University Belgrade; ⁶Mother and Child Health Care Institute of Serbia "dr Vukan Cupic"

⁷Mother and Child Health Care Institute of Serbia "dr Vukan Cupic", Medical Faculty, University Belgrade

⁸Mother and Child Health Care Institute of Serbia "dr Vukan Cupic", Medical Faculty, University Belgrade, Belgrade, Serbia

⁹Clinical Centre of Serbia, Clinic for Neurosurgery, University Clinical Center of Serbia, Neuro-Oncology, Belgrade, Serbia

¹⁰Clinical Center of Serbia, Clinic for Neurosurgery, Clinic for Neurosurgery, University Clinical Center of Serbia, Neurooncology, Belgrade, Serbia;

¹¹Medical Faculty, University Belgrade; ¹²Clinic for Endocrinology, School of Medicine, University of Belgrade, Medical Faculty, University of Belgr, Belgrade, Serbia;

¹³Clinic of Endocrinology, Neuroendocrine Department, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia, Belgrade, Serbia;

¹⁴Institute of Pathology, Neuropathology, Institute for Pathology, Medical Faculty, University Belgrade, Belgrade, Serbia;

¹⁵Neuroendocrine Department, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia;

¹⁶Clinic for Endocrinology, Diabetes and Metabolic Diseases - University Clinical Centre of Serbia, Neuroendocrinology, Belgrade, Serbia;

¹⁷Clinic for Neurosurgery, University Clinical Center of Serbia, Medical Faculty, University Belgrade, Belgrade, Serbia;

¹⁸Institute for Medical Statistics and Informatics, School of Medicine, University of Belgrade, Belgrade, Serbia, Institute of Medical Statistics and Informatics, Belgrade, Serbia, Serbia

¹⁹Department of Neuroendocrinology, Clinic for Endocrinology, Clinical Center of Serbia & School of Medicine, University of Belgrade, Neuroendocrine Department, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia, Belgrade, Serbia

Introduction: Adolescent transition to adulthood is a vulnerable period for pituitary diseases patients and particularly for CO-GHD survivors of cranial tumors or hematological malignancies.

Patients and Methods: In a monocentric, observational, retrospective cross-sectional study spanning 18 years, we analyzed 243 CO-GHD patients (16-26 years old, 168 males) at time-point of pediatric to adult endocrine care transfer and over transition period on GHR. Forty-nine subjects experienced childhood-onset cranial tumor or hematological malignancies (TUM, 49/20.1%). Other patients had congenital (CON, 105/43.2%) or idiopathic COGHD (IDI, 89/36.5%), Craniopharyngiomas predominated among TUM (38.7%; 19/49), followed by medulloblastoma and Langerhans cell histiocytosis (each 12.2%; 6/49), germinoma, astrocytoma and acute lymphoblastic leukemia - ALL (each 8.1%, 4/49), pituitary pseudotumor (TSH hyperplasia- 4.0%, 2/49), PNET, ganglioglioma, hamartoma and malignant triton tumor (2.0%, 1/49 each). In the acute phase of their causative illness, they were treated by surgery (88%), chemotherapy (45%) and radiotherapy (58%). We monitored possible tumor recurrence using cranial MRI and hematological evaluation every 6-12 months in TUM group. Monitoring for recurrent lesions on GHR also extended to 6 of CON patients who underwent non-cranial childhood surgery due to benign tumors of kidney (2), skin (2) adrenals (1) or mediastinum (1).

Results: Median age of patients (n=243) at time of transfer was 18.6 ± 2.8 years. TUM group was characterized by multiple anterior pituitary hormone deficiencies (92.0%). GH/IGF-I axis recovered in 33%, upon retesting at adult endocrine care. This recovery was most prevalent in the IDI (78%), while CON and TUM groups reverted GHD in 10.8% and 7.6%, respectively. Patients with persistent GHD continued GHR in daily doses of 0.5 ± 0.2 mg (range 0.3-1.4mg) with follow-up IGF-I maintained mid-ranged. Start of treatment was at 17.2 ± 1.6 , 19.3 ± 2.7 and 18.7 ± 2.8 years and the average duration of this treatment was 7.2 ± 3.8 , 6.8 ± 3.1 and 6.0 ± 2.4 years in TUM, CON and IDI group ($p > 0.05$) in transition period, respectively. During GH replacement no cranial tumor recurrence or ALL relapse was detected in TUM group nor benign tumors regrowth in the CON group.

Conclusion: In the 49 evaluated patients with CO-GHD related to cranial tumor or hematological malignancy, a high level of safety of GH replacement in transition period has been demonstrated. No tumor recurrence or disease relapse was found in any of the subjects over the average 7.2 years of GH replacement follow-up.

Abstract-ID: 144

IMPLICATION OF USP8 MUTATIONS IN THE PATHOGENESIS OF SILENT CORTICOTROPH TUMORSANTONIO PICO¹, Johana Sottile², Luis Valor³, MIGUEL EDUARDO GARCÍA GARCÍA⁴, Lucía Martínez⁵, María Eugenia Torregrosa⁶, Javier Abarca⁷, Cristina Lamas⁸, Raúl Luque⁹, Araceli García-Martínez¹⁰¹University Miguel Hernandez, Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Endocrinology & Metabolism, Alicante, Spain²Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Endocrinology & Metabolism, Alicante, Spain³Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Hospital General Universitario, Dr. Balmis, Alicante, Spain⁴Imibic, Instituto Maimónides de Investigación Biomédica de Córdoba (Imibic), University of Cordoba, Cordoba, Spain⁵Hospital General Universitario Dr. Balmis, Pathology, Spain⁶Hospital General Universitario Dr. Balmis, Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Clinical Analysis, Spain⁷Hospital General Universitario Dr. Balmis, Neurosurgery, Spain⁸Hospital General Universitario de Albacete, Endocrinology & Metabolism, Albacete, Spain⁹Instituto Maimónides de Investigación Biomédica de Córdoba, Physiology, Córdoba, Spain¹⁰Instituto Maimónides de Investigación Biomédica de Córdoba, Physiology, Spain

USP8 (Ubiquitin Specific Protease 8) mutations are well-known driver mutations in functioning corticotroph tumours. However, its relevance in silent corticotroph tumours (SCTs) is less known. The study **aimed** to provide insights into the role of USP8 mutations in silent corticotroph tumours (SCTs) and their impact on clinical parameters and gene expression profiles. **Methods:** We performed Sanger sequencing in 10 silent corticotroph tumours (SCT) coming from a unique PTCOE. We retrieved demographic and clinical variables (maxim tumour diameter, invasion, and proliferation) and analysed the expression of genes (qPCR) involved in the processing of ACTH (POMC, CHRH, AVPR1, TBX19, PCSK173, PCSK 2, PAM, CPE), in ACTH secretion (CABLES1, USP8, EGFR), in the glucocorticoid receptor activity (HSF1, AP-1) and the immune microenvironment (MSH6, PDL-1). **Results.** The study found that a huge portion (70%) of the examined SCTs had somatic USP8 mutations. These mutations were heterozygous and primarily located in exon 14 of the USP8 gene. They tended to be smaller in size and less invasive compared to non-mutated SCTs. Additionally, they were more commonly found in younger patients. The gene expression analysis revealed differences between mutated and non-mutated SCTs in several categories: 1. **Processing and Secretion of ACTH:** Mutated tumours showed higher expression levels of genes involved in the processing and secretion of ACTH, such as POMC, CHRH, AVPR1, TBX19, PCSK1/3, USB, CABLES1, and EGFR. 2. **Degradation of ACTH:** There were no significant changes in the expression of genes involved in the degradation of ACTH (PCSK2, PAM, CPE). 3. **Proliferation:** there was no significant difference in the rate of proliferation between the two groups of tumors. 4. **Glucocorticoid Receptor Activity:** The study did not find significant differences in the expression of genes related to the glucocorticoid receptor pathway (HSF1, AP-1). 5. **Immune Microenvironment:** Mutated tumors showed increased activity in the immune microenvironment, as indicated by higher PDL-1 expression. 6. **Other Genes:** Non-mutated tumors expressed higher levels of CASP8 and SSTR2 compared to mutated tumors, which could have implications for potential medical treatments. **Conclusions:** The study's findings suggest that USP8 mutations are common in SCTs and may lead to a more differentiated gene expression profile in these tumors, resembling functioning corticotroph tumors. Additionally, the differences in CASP8 and SSTR2 expression offer potential therapeutic opportunities for non-mutated SCTs.

Abstract-ID: 149

ARE THE PATHWAYS INVOLVED IN THE FUNCTION AND PROLIFERATION OF CORTICOTROPH TUMOURS DIFFERENT BETWEEN FUNCTIONING AND SILENT CORTICOTROPH TUMOURSJohana Sottile¹, Araceli García², Luis Valor³, Lucía Martínez⁴, María Eugenia Torregrosa⁵, Javier Abarca⁶, Cristina Lamas⁷, ANTONIO PICO⁸¹*Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Endocrinology & Metabolism*²*Instituto Maimónides de Investigación Biomédica de Córdoba, Physiology, Córdoba, Spain*³*Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Alicante, Spain*⁴*Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Hospital General Universitario Dr. Balmis, Alicante, Pathology, Alicante, Spain*⁵*Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Clinical Analysis, Alicante, Spain*⁶*Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Hospital General Universitario Dr. Balmis, Alicante, Neurosurgery, Alicante, Spain*⁷*Hospital General Universitario de Albacete, Endocrinology & Metabolism, Albacete, Spain*⁸*University Miguel Hernandez, Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Endocrinology & Metabolism, Alicante, Spain*

Silent corticotroph tumours are nearly 30 % of all pituitary tumours of the corticotroph line. The reason because some corticotroph tumours (CT) do not express Cushing disease is not well-known. Methods: We analysed two cohorts of corticotroph tumours: 18 functioning (FCT) and 20 silent (SCT). We retrieved demographic and clinical variables (maximum tumour diameter (MTD), invasion, and proliferation) and analysed the expression of genes (qPCR) involved in the processing/degradation of ACTH (POMC, CHRH, AVPR1, TBX19, PCSK173, PCSK 2, PAM, CPE), ACTH secretion (CABLES1, USP8, EGFR), the glucocorticoid receptor activity (HSF1, AP-1) and in the immune microenvironment (MSH6, PDL-1).

Results: 61 % and 50 % of patients with FCTs and SCTs were women, respectively. There was no significant difference in age (43.4 vs. 46.8 years) between the two cohorts. SCTs were significantly higher (median MTD 23 vs 10 mm; $p=0.02$, respectively), more invasive (68,42 vs. 37.5 %), and more proliferative (Ki67 (%) 2.06 vs 1.67, $p=0.59$) than FCTs. SCTs showed lower expression of the genes involved in the processing and secretion of ACTH (POMC, CHRH, AVPR1, TBX19; PCSK 1/3, USP8, CABLES 1, EGFR) and more ACTH degradation (PCSK2, CPE) than FCTs, although without significance. There were no differences between groups in the genes involved in the GR pathway (HSF1, AP-1) nor in the immune microenvironment (MSH6/PDL-1). Contrarily, FCTs expressed more SSTR2 (median FC 0.15 vs 0.007 ($p=0.024$)) but not SSTR5 (mean 0.21 vs 0.214; $p=0.97$) than SCTs. Finally, 4/13 (30 %) FCTs and 7/10 (70%) SCTs showed USP8 mutations. **Conclusion:** A low production of ACTH seems the main silencing mechanism of the tumours of the corticotroph lineage which do not associate with Cushing Disease

Abstract-ID: 150

IS IT POSSIBLE TO ANTICIPATE THE DIAGNOSIS OF SILENT CORTICOTROPH TUMOURS BEFORE SURGERY?

Cristina Guillen¹, Johana Sottile², Elena García-Garrigós³, Victoria González⁴, Ana Flores⁵, Luís Concepción⁶, Joaquín Serrano⁶, ANTONIO PICO⁷

¹*Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Hospital General Universitario Dr. Balmis de Alicante, Endocrinology & Metabolism, Alicante, Spain*

²*Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Endocrinology & Metabolism, Alicante, Spain*

³*Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Hospital General Universitario Dr. Balmis, Alicante, Radiology, Alicante, Spain*

⁴*Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Hospital General Universitario Dr. Balmis, Alicante, Clinical Analysis, Alicante, Spain*

⁵*Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Neurosurgery, Alicante, Spain*

⁶*Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Hospital General Universitario Dr. Balmis, Alicante, Alicante, Spain*

⁷*University Miguel Hernandez, Instituto de Investigación Sanitaria Y Biomédica de Alicante (Isabial), Endocrinology & Metabolism, Alicante, Spain*

Silent pituitary tumors are defined prior to surgery as Non-Functioning Pituitary Adenomas (NFPAs). The majority of NFPAs are silent gonadotrophic tumors (SGTs), secondly, silent corticotroph tumors (SCTs). The definitive diagnosis is made by pathological analysis after surgery. However, the behavior of these subtypes is different and their identification before surgery can be important for its management and for research studies such as cellular cultures.

Aim: The aim of this study was to compare and identify characteristics between SGT and SCT to be able to establish an accurate diagnosis previously of conducting surgery.

Methods: Retrospectively we studied two cohorts of NFPA coming from a unique PTCOE identified after surgery as SCT (n=20) and SGT (n=42) in our cohort of PitNETs. We have analysed the following variables: age, sex, tumor size, invasion grade, basal levels of LH, FSH, ACTH, and cortisol, and radiological characteristics (T2-Signal Intensity Ratio, (SIR)) of the tumours in Magnetic Resonance Images (MRI).

Results: 50 % of the SCTs and 36.59 % of SGTs were women. Patients with SCTs were significantly younger (median 50 vs. 60 years; p=0,0019). There were no differences in the tumor size (DMT mean 25,56 vs. 29,46 mm, respectively, p=0.18). Signal Intensity Ratio (SIR) was higher in SCTs than in GTs (median 2.56 vs 1.87, respectively, p=0.0015). Moreover, SCTs were slightly more invasive than SGTs (68.42 vs. 60.5 %) and showed more recurrences (4/16 (25 %) vs. 4/42 (9 %), respectively). There were no differences in the levels of cortisol (mean 12.5 vs 1.8 mcg/dl; p= 0.47), FSH (mean 9.7 vs 11.2 U/L, p=0.77) or LH (mean 6.4 vs 4.1 U/L, p=0.32). Only ACTH was different (median 41.4 vs 24.0 pg/ml, SCTs vs SGTs p=0.003).

Conclusions: A woman under 50 years, with a pituitary tumour with a T2-weighted image SIR > 2, and ACTH levels greater than 30 pg/mL, should be considered a carrier of a silent corticotroph tumour and her surgery should be prioritized.

Abstract-ID: 156

THE OUTCOME OF PITUITARY APOPLEXY IN SECRETING PITUITARY ADENOMAS

Monica Livia Gheorghiu¹, Oana Iana², Simona Jercalau², Corin Badiu³

¹*C.I. Parhon National Institute of Endocrinology, Carol Davila University of Medicine and Pharmacy, Endocrinology, Bucharest, Romania*

²*C.I. Parhon National Institute of Endocrinology, Bucharest, Romania*

³*National Institute of Endocrinology, "C.Davila" University of Medicine, Carol Davila University of Medicine, Bucharest, Romania*

Pituitary apoplexy (PA) is a rare syndrome due to a clinically overt hemorrhagic infarction, described in 2-7% of pituitary adenomas, mostly in nonfunctioning pituitary adenomas.

Aim of study. To assess the outcome of PA in patients with secreting pituitary adenomas.

Methods. A retrospective review of patients with secreting pituitary adenomas hospitalized between 2005 - 2023 revealed 16 consecutive cases with PA diagnosed based on clinical symptoms, imaging and pathology description.

Results. Sixteen patients (12 prolactinomas, 3 acromegaly and 1 Cushing's disease), 5 women, 11 men, mean age at diagnosis 34.8 years (range 21 – 55 years), all with macroadenomas at the diagnosis of PA; only 3 (18.7%) had been diagnosed and treated before the occurrence of PA. Visual impairment was recorded in 12/16 (75%), pituitary insufficiency of at least one hormonal line in 12/15 (80%). Pituitary surgery was undertaken in 12/16 (75%), 4 patients have been treated conservatively, 2 of those being women during pregnancy. In 13/16 patients (81%) the hypersecretion continued after PA, remission was recorded in 3 patients (18.7%), all women.

Case 1. Cushing's disease, previous bilateral adrenalectomy, tendency to Nelson's syndrome, pregnant in 22 weeks when the PA occurred (treated with iv glucocorticoids 3 days); ACTH decreased from 911 to 5.6 pg/mL (N 3-66), then increased to normal in the next 2 years, afterwards to 100 – 280 pg/mL (acceptable range for the patient's primary adrenal insufficiency), stable for 13 years after PA. She had GH and gonadotroph insufficiency after PA.

Case 2. A woman with clinical acromegaly and a conservatively treated (but not clearly diagnosed) PA (with transient VI nerve palsy, 2 cm pituitary mass), presented 1 year later with thyrotropin, gonadotropin and partial corticotropin insufficiency and a 0.5 cm pituitary mass; she had normal IGF1 and a nadir GH in OGTT decreasing from 1.8 to 0.4 ng/mL in the next 2 years. IGF1 started to increase 13 years later up to 1.35xULN at 19 years, nadir GH 0.5 ng/mL, stable pituitary mass.

Case 3. A woman with acromegaly and PA underwent transphenoidal surgery, with no tumor remnant and normal IGF1 and GH 3 months after surgery (+ central hypothyroidism and hypogonadism). A mild IGF1 increase occurred during the next 4 years up to 1.36xULN, while nadir GH remained < 1 ng/ml, and new small pituitary masses became visible on MRI.

Conclusion. Pituitary apoplexy occurs rarely in secreting pituitary tumors, but it may lead to their diagnosis. Remission of the hypersecretion after PA is rare and may be followed by late recurrency, therefore long-term follow-up is needed in these patients.

Abstract-ID: 160

CHANGES IN WEIGHT AND BMI FOLLOWING TREATMENT FOR CUSHING SYNDROME: LONG-TERM OUTCOMES AND POTENTIAL PREDICTORS

Amit Akirov¹, Yaron Rudman², Shiri Kushnir³, Laura Dery⁴, Ilan Shimon⁵, Liat Sasson²

¹Rabin Medical Center, Beilinson Campus, Petah-Tikva, Israel

²Beilinson Hospital, Rabin Medical Center, Institute of Endocrinology, Petah Tikva, Israel

³Beilinson Hospital, Rabin Medical Center, Research Authority, Petah Tikva, Israel

⁴Sackler School of Medicine, Tel Aviv University, Israel

⁵Institute of Endocrinology, Beilinson Hospital, Sackler School of Medicine, Tel Aviv University, Israel

Background: In patients presenting with Cushing syndrome (CS), weight and total body fat are higher than matched controls. We aim to assess the changes in weight and body-mass index (BMI) following treatment for CS and identify potential predictors for weight loss.

Methods: Using the Clalit Health Services database, we retrospectively studied a cohort of CS patients and age-, sex-, BMI-matched controls (1:5 ratio). Weight and BMI were determined at baseline, one year after diagnosis, and at the end of follow-up.

Results: The study cohort included 345 patients (63.6% women, mean age 54.2±16.40 years). One year after diagnosis (n=280), weight decreased from 85.2±22.4 to 82.1±21.7 kg (p<0.01), and BMI decreased from 31.3±7.6 to 29.9±7.1 kg/m² (p<0.01). Among 160 patients who attained remission within a year, weight decreased from 84.60±21.41 to 81.21±20.93 kg (p<0.01), and BMI decreased from 31.32±7.38 to 29.76±6.97 kg/m² (p<0.01).

No differences in BMI and weight were noted in patients who did not achieve remission after one year. Among 174 patients who attained remission by the end of 8.6 years of follow-up, BMI decreased from 30.81±7.58 to 28.86±7.64 kg/m² (p<0.01), and weight decreased from 82.87±21.53 to 78.62±24.92 kg (p<0.01), with weight reduction ≥5% in 47.7% of patients and ≥10% in 33.3%.

Patients who did not achieve remission at the end of follow-up did not see changes in BMI and weight. Analysis according to CS etiology indicated that among patients with pituitary CS, remission was associated with a decrease in BMI (30.44±7.36 to 28.27±6.59 kg/m², p<0.01) and weight (83.78±22.68 to 77.95±20.7 kg, p<0.01), while BMI and weight were unchanged in those who did not attain remission. Among those with adrenal CS (n=78), remission was associated with a decrease in BMI from 30.99±7.81 to 28.74±6.79 kg/m² (p=0.01), and weight from 81.81±21.23 to 77.99±20.79 kg (p=0.03). A milder weight reduction was achieved in adrenal CS patients who did not achieve remission.

Multivariate analysis identified female gender (odds ratio [OR] 1.81, 95% CI, 1.04-3.13), baseline BMI ≥30 (OR 1.74, 95% CI, 1.02-2.98), BMI decrease of ≥1 kg/m² at 1 year (OR 4.63, 95% CI, 2.67-8.03) and dyslipidemia (OR 2.16, 95% CI, 1.09-4.27) as predictors of ≥5% weight loss.

Conclusion: Approximately half of CS patients who attained disease remission achieved at least a 5% decrease in BMI with long-term follow-up. Disease remission, female gender, baseline BMI ≥30, BMI decrease of ≥1 kg/m² at 1 year, and the presence of dyslipidemia predict a clinically significant weight loss.

Abstract-ID: 183

IMPAIRMENTS IN CARBOHYDRATE EXCHANGE IN PATIENTS WITH HORMONALLY ACTIVE ADRENAL NEOPLASMS

Gulrukh Alimoukhamedova¹, Zamira Khalimova², Tursunoy Odilova²

¹Republican Specialized Scientific-Practical Medical Centre of Endocrinology, Republican Center of Endocrinology, Tashkent, Uzbekistan

²Academician Yo. Kh. Turakulov Center for the Scientific and Clinical Study of Endocrinology, Tashkent, Uzbekistan

Materials and methods

The material for the study was observation of 121 patients with hormonally active adrenal neoplasms who were treated at the Republican Specialized Scientific Practical Medical Center of Endocrinology named after Academician E.H. Turakulov. Among them there were 51 (42.2%) with pheochromocytoma, 45 (37.2%) with corticosteroma, 16 (13.2%) aldosterone-producing adenoma (APA) and 9 (7.4%) with androsteroma. In the control group there were 24 patients without arterial hypertension (AH) and 22 patients with AH without adrenal gland neoplasms, similar in age and gender to the main group.

All the patients with adrenal neoplasms underwent general clinical, biochemical, hormonal and instrumental studies according to the standard methodology.

Results and discussion

Out of 51 patients with pheochromocytoma disorders of carbohydrate metabolism (DCM) were detected in 9 (17.6%; $\chi^2=40.2$; $p<0.0001$), and 8 (15.7%; $\chi^2=45.3$; $p<0.0001$) of them had diabetes mellitus (DM). Analysis of fasting glycemia indicators averaged 4.95 ± 1.4 mmol/l, and 2 hours after eating 5.21 ± 1.6 mmol/l. We did not find significant differences in fasting glycemia and 2 hours after meals in the comparison groups. Glycated hemoglobin ($5.37\pm 1.9\%$) was higher in the main group than in the groups without ($4.70\pm 0.59\%$) and with hypertension ($4.93\pm 0.26\%$), but no significant differences were found. One patient (2.0%) had violation of fasting glycemia (FG).

Among the patients with corticosteromas DCM were observed in 29 (64.4%). The average levels of fasting glycemia in this group were 5.94 ± 1.9 mmol/l, and two hours after meals 8.42 ± 3.4 mmol/l, with glycated hemoglobin $6.07\pm 0.9\%$. Of these 11 (24.4%) developed steroid DM, 12 (26.7%) disturbed fasting glycemia, and 6 (13.3%) impaired glucose tolerance. All indicators of carbohydrate metabolism were statistically significant ($p<0.001$) in relation to both control groups.

In the group of the patients with APA the indicators of fasting glycemia and glycemia 2 hours after meals, as well as glycated hemoglobin, were significantly higher compared to the control groups without and with hypertension. At the same time 3 (18.8%) patients had DM, and other 2 (12.5%) had disturbed fasting glycemia. There were no other types of DCM among the patients with APA.

According to the literature, there are no significant metabolic disorders among patients with androsteroma. In our observations glucose level in the androsteroma group 2 hours after eating was statistically significantly higher ($p<0.001$) than in both control groups, but it remained within the normative values.

Conclusions

Thus, among the patients with hormonally active adrenal tumors more than a third (36%) had various types of DCM, while the greatest disturbances in carbohydrate exchange were detected in patients with cortisol-secreting tumors.

Abstract-ID: 189

MALIGNANT TUMORS IN THE STRUCTURE OF ADRENAL NEOPLASMS

Gulrukh Alimoukhamedova¹, Zamira Khalimova², Tursunoy Odilova²

¹Republican Specialized Scientific-Practical Medical Centre of Endocrinology, Republican Center of Endocrinology, Tashkent, Uzbekistan

²Academician Yo. Kh. Turakulov Center for the Scientific and Clinical Study of Endocrinology, Tashkent, Uzbekistan

The present study is based on clinical observations of 282 patients with various neoplasms of adrenal glands who were treated at the Republican Specialized Scientific Practical Medical Center of Endocrinology named after Academician E.H. Turakulov.

All patients with adrenal gland neoplasms underwent general clinical, clinical-biochemical, hormonal and instrumental studies.

Results and discussion

In the group of 282 patients with various neoplasms of adrenal glands malignant tumors accounted for 16 (5.7%), of which there were 5 (1.8%) patients with manifest ACC and 11 (3.9%) with metastatic tumors of adrenal glands. The average age of the patients with malignant tumors of adrenal glands was 50.7 ± 14.5 years old. At the same time, the average age of the patients with manifest ACC was 49.0 ± 20.9 years old, and with metastatic adrenal tumors 51.5 ± 11.8 . The most common malignant tumors were found in middle-aged patients (45-59 years) with 43.8%. Unlike the rest of the groups we studied with adrenal gland neoplasms, men (75%) prevailed in this group, while women made up only a quarter.

At the onset of the disease 6 (37.5%) patients had intense pain in the abdomen or lumbar region, while 18.8% of the patients at the beginning of the disease noted progressive weight loss in combination with general weakness. In other 6 (37.5%) patients the disease manifested pain in the abdomen or lumbar region combined with progressive body weight loss. Only in one case in a patient with manifest ACC the disease debuted with increase in blood pressure.

A study of the hormonal background revealed statistically significant difference in the levels of DGEA in the patients with malignant tumors of adrenal glands compared with control groups with both hypertension and without hypertension.

During MSCT of adrenal glands done with contrast the average APW and RPW values in the patients with malignant tumors were $51.7 \pm 13.6\%$ and $26.0 \pm 5.0\%$, respectively. According to MSCT data with contrast enhancement APW $\leq 60\%$ and RPW $\leq 40\%$ were found in 88.9% and 100% of patients, respectively.

Conclusions

Adrenal malignancies were more common in middle-aged patients (45-59 years) with 43.8%, with predominance among men (75%). Almost all patients presented nonspecific complaints of abdominal or lumbar pain (15-93.8%), general weakness (15-93.8%), weight loss (15-93.8%), and fatigue (14-87.5%). When analyzing the level of DGEAS in the patients with malignant tumors of adrenal glands, a statistically significant difference was found compared with the control groups both with and without arterial hypertension. According to MSCT data with contrast enhancement APW $\leq 60\%$ and RPW $\leq 40\%$ were found in 88,9% and 100% of the patients, respectively.

Abstract-ID: 210

EFFECTIVE TREATMENT OF PITUITARY MICROADENOMA USING IRANIAN CABERGOLINE: A CASE STUDY

Narges Kashanivahid¹, Hadi Tabesh¹, Farahnaz Soltanian Zadeh², Hamid Bazrafshan³

¹*Department of Life Science Engineering, Faculty of New Sciences and Technologies, University of Tehran, Tehran, Iran*

²*Dr. Bazrafshan Thyroid and Pituitary Clinic, Tehran, Iran*

³*LMU, Golestan University ,, Neuro-Endocrinology, München, Germany*

Introduction:

Treatment of pituitary microadenoma is generally difficult and time consuming. Dopamine agonist therapy is usually attempted first for a period of several months. If the tumors do not respond to medication therapy, then surgery is considered. However, appropriate therapy to avoid surgery is challenging.

Method:

A 23-years old female patient with 164 cm height and 48 kg weight visited Dr. Bazrafshan Clinic with chief complaint of low gain weight. After receiving of her medical history and general nutrition diet, a full blood experiment was ordered. The results demonstrated remarkable elevations of prolactin and IGF1 of 49 ng/ml and 258.5 ng/ml respectively. Then, the patient was sent for MRI. The results indicate a 2*3 mm microadenoma in the central part of pituitary. A medical treatment with ¼ Cabergoline 1 mg twice a week at night for the first month and then ¼ Cabergoline 1 mg once a week at night for the next 2 months with a full blood test at the end of this 3-months period was ordered. The Cabergoline administration dosage was reduced in the flowing 3-month treatment period due to the plasma level prolactin.

Results:

The plasma prolactin level was sharply decreased to 24.4 ng/ml (normal range: 4.5-24) and the plasma IGF1 level to 180 ng/ml (normal range: 99-180). Due to the blood examination results, for the treatment period, ¼ Cabergoline 1 mg in addition to ¼ Dexamethasone 8 mg once in each 10-days at night with a full blood test at the end of this period was prescribed. The results revealed that the prolactin plasma level was further decreased to 7.6 ng/ml within the normal range. In the last MRI investigation, post-treatment, no trace of microadenoma was reported in the pituitary gland.

Conclusion:

The administration of a proper Cabergoline dosage in addition to the timely diagnosis and regular follow up could be considered effective in patients suffering from pituitary microadenoma.

Abstract-ID: 219

THE ENDOSCOPIC ENDONASAL RESECTION OF GIANT PITUITARY NEUROENDOCRINE TUMORS - CASE SERIES FROM THE REFERRAL PITUITARY CENTER.

Barbara Buchalska¹, Maria Maksymowicz², Jacek Kunicki³

¹The Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland, Department of Neurosurgery

²The Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland, Department of Pathology

³The Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland, Department of Neurosurgery, Warsaw, Poland

Introduction: The Giant Pituitary Adenomas (GPAs) are still a challenging surgical problem. They comprise 6-15% of operated pituitary adenomas. The advances of an endoscopic technique allow the resection of pituitary tumors previously operated by transcranial approaches. The aim of the study was to review the surgical results in a series of patients with GPAs operated with endoscopic endonasal approach.

Material and methods: The study is a retrospective analysis of a series of 170 patients (65 women and 105 men) treated from the 2007 to 2023 by the endoscopic transsphenoidal surgeries for GPAs (>40mm). The mean age of the patients was 57.1 years (20-81 years), and the mean follow up period was 7.1 years (0-16 years). Thirty-seven patients had 1a grade of the classification proposed by Trouillas, 6 patients – 1b, 96 patients – 2a, and 18 patients – 2b.

Results: The gross total resection was accomplished in 76 out of 170 cases (44.7%), the subtotal resection was achieved in 67 of 170 patients (39.4%), in 26 cases (15.3%) only the partial resection was possible. Extended endoscopic approaches were used in 12 patients (7.1%), 66 patients had an intra-operational cerebrospinal fluid leak, and 106 patients had a reconstruction of the sella turcica with an adipose tissue graft. There were two mortalities in the series. Postoperatively 61.0% of the patients showed varying improvement in visual field defects and visual acuity. Transient diabetes insipidus (DI) was observed in 22 patients (12.9%). The postoperative CT scan revealed significant intrasellar/suprasellar hematoma in 11 (6.5%) patients and 7 of them were reoperated. The CSF leak was observed in 5 cases (2.9%). There were 7 cases of visual function deterioration in the series. During a mean 7.3 years observation there were 35 (20.6%) cases of recurrences.

Conclusions: Our results indicate that resection with endoscopic endonasal approach can be a safe and effective method for the treatment of patients with giant pituitary adenomas and it is the alternative for transcranial approaches.

Abstract-ID: 224

CLINICOPATHOLOGICAL ANALYSIS AND OUTCOMES OF THYROTROPHE PITUITARY NEUROENDOCRINE TUMORS (TSH IMMUNOPOSITIVE ADENOMAS).

Jakub Skiba¹, Maria Maksymowicz², Jacek Kunicki³

¹The Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland, Department of Neurosurgery

²The Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland, Department of Pathology

³The Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland, Department of Neurosurgery, Warsaw, Poland

Background: TSH pituitary neuroendocrine tumors (PitNET)s, are a rare type of tumor (1 - 3%), derived from Pit1 transcription factor line. The aim of the study was to analyze the results of surgical treatment, invasive character and the clinical and pathological characteristics of new various types of PitNETs that can secrete TSH.

Methods: The study is a retrospective analysis of patients diagnosed with thyrotrophe pituitary neuroendocrine tumors(TSH-secreting adenomas) . TSH Pitnet were defined as those with immunohistochemical staining for TSH, even if they also stained for other hormones. During 2005-2022, 39 patients were treated with transsphenoidal endoscopic surgery at the Department of Neurosurgery. Those patients accounted for 1.55% of the operated adenoma cases.

Results: Our group consisted of 39 cases (26 women and 13 men) The mean age at diagnosis was 48 aged (range 19 to 47) . There were 33 macroadenomas, 4 giant adenomas and 2 microadenomas. The most frequently reported symptoms were headache (56%) and visual disturbances (31%). Central hyperthyroidism was diagnosed in 10 (26%) patients. Twenty seven tumors (69%) stained for other hormones, 8 of which were classified as immature Pit1-lineage PitNETs and 13 mature plurihormonal PIT1-lineage PitNETs. Invasive growth (suprasellar invasion, Knosp III and IV) was observed in 6 (75%) immature Pit1 PitNETs, 6 (46%) mature plurihormonal PIT1 PitNETs and 7 (39%) thyrotroph tumors. Surgical results : 33 patients (85%) achieved complete resection confirmed by MR examination. There were no serious complications or deaths: transient diabetes insipidus - 4, cerebrospinal fluid leakage - 2, SIADH – 1, paresis of the oculomotor nerve - 1.

Conclusions: Thyrotrophe pituitary neuroendocrine tumors are rare tumors that typically present as macroadenomas, in majority not presenting with primary hyperthyroidism . Surgical treatment of immunopositive TSH PitNETs by transsphenoidal endoscopic methods is a safe and highly effective method. The factors limiting the effectiveness of surgical treatment are the invasive growth and the multi-hormonal nature of the tumor

Abstract-ID: 260

CHARACTERISTICS OF GROWTH AND DEVELOPMENT OF ADOLESCENTS WITH CONGENITAL AND ACQUIRED MULTIPLE PITUITARY HORMONE DEFICIENCYUtkir Mavlonov¹, Urmanova Yulduz²¹*Bukhara Endocrin Ambulance, Diabetology, Bukhara, Uzbekistan*²*Tashkent Paediatric Medical Institute, Republican Scientific-Practical Medical Center of Endocrinology, Scientific, Tashkent, Uzbekistan*

INTRODUCTION Multiple pituitary hormone deficiency (MPDH) means that the anterior pituitary gland fails to produce several hormones, often including growth hormone and others. There are two types of MDDH: acquired and congenital. Acquired MDDH can be a consequence of birth trauma, brain contusion, radiation therapy or surgery on the pituitary gland. Congenital MDDH is a rare disease caused by mutations in the pituitary transcription factor genes: PROP1, POU1F1 (PIT1), HESX1, LHX3, LHX4.

In the literature, in most cases, the differentiation of congenital and acquired MPDH is not made, and the clinical picture for each group is usually not mentioned.

THE PURPOSE OF THE STUDY is to study the characteristics of patients with congenital and acquired multiple pituitary hormone deficiency.

MATERIALS AND METHODS OF RESEARCH. We examined and examined 19 patients suffering from MDDH. Of these, there were 9 girls and 11 boys. The average age of boys was 12.6 ± 1.2 years, and the average age of girls was 12.3 ± 1.6 years. 20 healthy adolescents of the appropriate age formed the control group.

The patients were divided into 2 groups: group 1 – patients with acquired MDH – 9 patients, group 2 – patients with congenital MDH – 9 patients. The control group consisted of 20 healthy adolescents of the corresponding age.

All 18 patients underwent all studies, including general clinical (general blood count, general urine test, etc.), biochemical, hormonal blood tests (STH, FSH, LH, ACTH, TSH, PRL, free thyroxine, cortisol, progesterone, estradiol, free testosterone), as well as instrumental - ECG, ultrasound of internal and genital organs, MRI of the pituitary gland, etc.

RESEARCH RESULTS. Between groups 1 and 2, there were no differences in such indicators as RPR, VPR, passport age between groups 1 and 2 and in comparison with the control. At the same time, the most pronounced lag in physical development was observed in patients of group 2. Bone age was significantly behind the norm in both groups ($p < 0.05$), higher in the 2nd group. Growth velocity, growth velocity SDS, height, height SDS, weight, weight SDS were significantly lower

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A CASE OF LACTOTROPH CARCINOMA ESCAPING TEMOZOLOMIDE RESPONSE AND UNRESPONSIVE TO PEMBROLIZUMAB

Sylvère Störmann¹, Felix Amereller², Katharina Schilbach³, Jochen Schopohl⁴

¹*Klinikum der Universität München, Medizinische Klinik und Poliklinik IV, München, Germany*

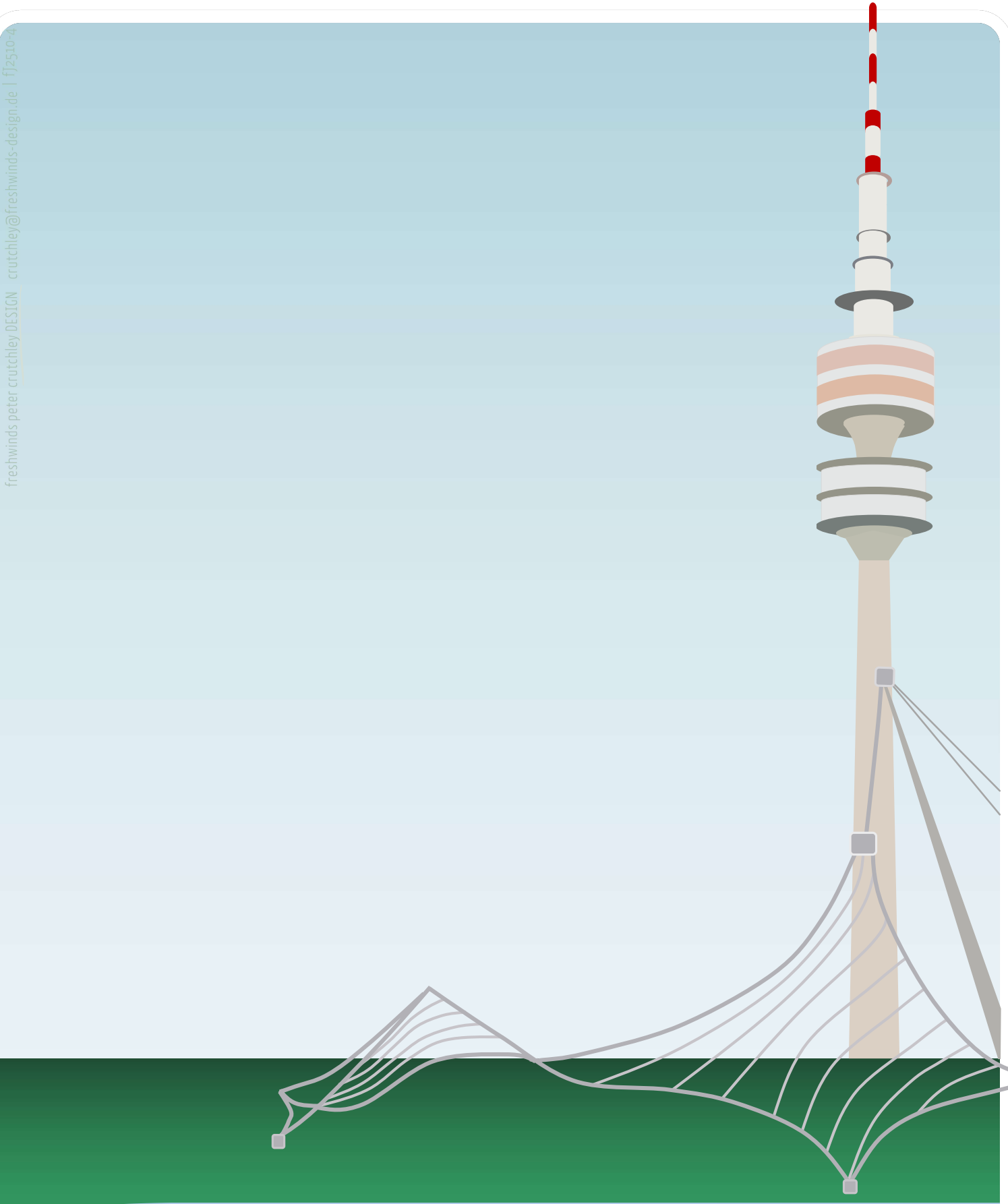
²*Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Klinikum der Universität München, München, Germany*

³*Med. Klinik & Poliklinik IV, LMU Klinikum, Medizinische Klinik und Poliklinik IV, München, Germany*

⁴*Medizinische Klinik IV, Lmumünchen, LMU Klinikum, München, Neuroendocrinology, Munich, Germany*

Introduction: Lactotroph tumors are the most prevalent form of functioning pituitary adenomas and usually respond well to treatment with dopamine agonists. Aggressive forms and carcinomas exist that may respond well to temozolomide (TMZ). We report the case of a patient successfully treated with TMZ for several years before severely progressive disease occurred.

Case Report: In 2013 episodic headaches occurred in our patient at age 54 and subsequent diagnostics revealed a macroprolactinoma. Dopamine agonist treatment with cabergoline was initiated and up-titrated up to 1 mg/d, but the tumor progressed and was surgically removed one year later. Histopathology confirmed an atypical adenoma with a high proliferation marker Ki-67 of 30%. Clinically, the patient's headaches improved after debulking and radiotherapy. As of 2016 the patient gradually developed severe back pain due to spinal metastasis of the pituitary lesion, thus confirming a lactotroph carcinoma. Initial treatment with cisplatin and etoposid didn't have any effect. Radiotherapy of a metastasis in the cervical spine followed with short-term reduction of prolactin levels. As of April 2018 TMZ was started inducing remission with complete normalization of prolactin levels within the first 12 months of therapy. Remission was sustained until the end of 2020. Two new spinal metastases were detected and surgically removed with post-operative radiation. Despite increases of TMZ dose the prolactin levels continued to rise rapidly without discernible tumor in imaging. Only in September 2021 metastases between T12 and L4 could be detected with MRI and FDG PET. The addition of pasireotide induced a temporary reduction of prolactin levels, but the tumor continued to progress rapidly with disability and a steep decline of the general condition. In November 2021 a spinal metastasis of approximately 5 cm between L2 and L4 and disseminated metastases were found. Next generation sequencing of the samples from 2020 yielded a mutation in the ARID 2 gene, suggesting possible response to pembrolizumab treatment. A therapy with 2 mg per kg body weight of pembrolizumab was initiated but to no avail. Fast growing intracerebral metastases developed. The patient's condition deteriorated further and he ultimately died in February 2022.



ILLUSTRATIONS:
Marily Theodoropoulou

