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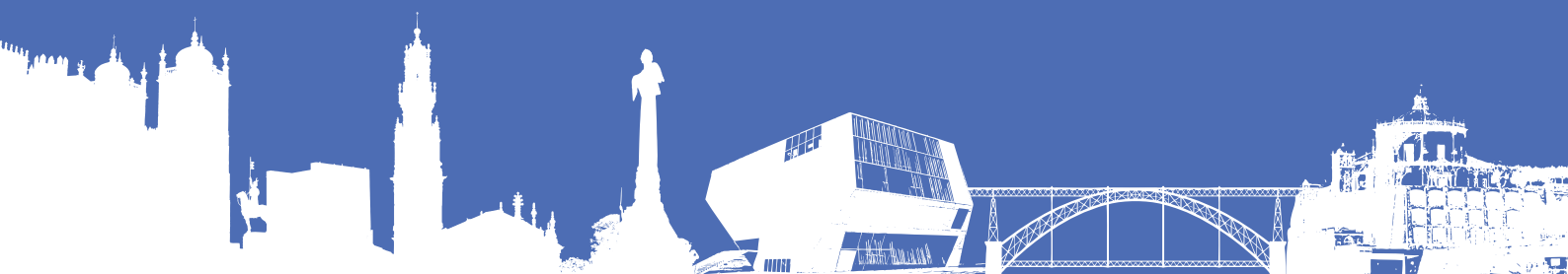

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CONGRESS ABSTRACTS

Oral Communications

OC-01 - DETERMINANTS FOR LONG-TERM REMISSION AFTER TRANSSPHENOIDAL SURGERY IN CUSHING'S DISEASE

Sílvia Santos Monteiro (Portugal)[1]; Ana Lopes (Portugal)[1]; Liliana Fonseca (Portugal)[1]; Vânia Benido Silva (Portugal)[1]; Patrícia Rosinha (Portugal)[2]; Catarina Chaves (Portugal)[3]; Liliana Ferreira (Portugal)[1]; Isabel Ribeiro (Portugal)[4]; Cláudia Amaral (Portugal)[1]; Maria Helena Cardoso (Portugal)[1]

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Introduction: The gold-standard treatment for Cushing's disease (CD) is transsphenoidal surgery (TSS). Long-term clinical course of postsurgical remission or recurrent disease remains unclear, with significant variability in remission rates.
Aim: Identify predictors for long-term remission in patients with CD submitted to TSS.
Methodology: Retrospective cohort study, including patients with CD submitted to TSS in our tertiary center, between 1989 and 2019. Remission and recurrence rates of CD were evaluated, with a minimal follow-up of 12 months. Early remission (at 6 months after surgery) was considered when resolution of clinical suggestive of hypercortisolism and at least one of the following criteria: morning cortisol <5 µg/dL, serum cortisol <1.8 µg/dL after the 1mg dexamethasone suppression test (DST) or normal 24-hour urinary free cortisol (CLU). Sustained remission was assumed in patients who achieve postoperative remission criteria without evidence of disease relapse during follow-up. We evaluated possible predictors for long-term remission such as demographic variables, hormonal measurements, imaging and histological study.
Results: Fifty-five patients were included, with a mean age at diagnosis of 44±16 years and a mean follow-up of 9.3±7.1 years. The rate of early postoperative remission was 60% (n=33). In these patients, disease relapse during follow-up was documented in 9.1% (n=3), so a long-term sustained remission rate of 55% (n=30) was determined. An age below 44 years (67.8% *vs* 40.9%, *p*=0.05), lower mean plasma cortisol measurement after DST before surgery (8.1µg/dL *vs* 15.9 µg/dL, *p*=0,03), imagiological evidence of adenoma (64,1% *vs* 25%, *p*=0,02), complete macroscopical excision of the tumor (72% *vs* 28.6%, *p*=0.04), identification of ACTH-secreting adenoma on histological examination (68.4% *vs* 26.7%, *p*<0.01), hypocortisolism in the immediate postoperative period (87.5% *vs* 33.3%, *p*=0.03), lower mean postoperative nadir serum cortisol (2.7±0.6 µg/dL *vs* 16.4±2.3 µg/dL, *p*<0.01) and lower median concentration of ACTH in postoperative period (24.5 pg/mL *vs* 35 pg/mL, *p*=0,01) were factors associated with long-term sustained remission. We found no statistically significant differences in relation to the remission rate in patients with a lower CLU value prior to surgery (445µg/24h *vs* 267µg/24h, *p*=0,26), smaller dimensions adenoma (50% *vs* 73%, *p*=0,30), absence of invasion of adenoma (52.9% *vs* 75%, *p*=0.61), nor with pre-surgical medical treatment (69.2% *vs* 45.5%, *p*=0,17).
Conclusion: Age, pre-surgical post DST cortisol levels, imagiological evidence of adenoma, complete macroscopical excision of the tumor, histological evidence of ACTH-secreting adenoma, postoperative hypocortisolism and both postoperative nadir serum cortisol and ACTH concentration are important factors associated with long-term therapeutic success and disease remission.

OC-02 - TESOMET CAUSES SIGNIFICANT WEIGHT LOSS RESULTING IN REDUCED LEVOTHYROXINE REQUIREMENTS IN HYPOPITUITARY PATIENTS WITH ACQUIRED HYPOTHALAMIC OBESITY

Kim Huynh (Denmark)[1]; Marianne Klose (Denmark)[1]; Kim Krogsgaard (Denmark)[2]; Joergen Drejer (Denmark)[3]; Sarah Byberg (Denmark)[6]; Sten Madsbad (Denmark)[4]; Faidon Magkos (Denmark)[5]; Berit Edsberg (Denmark)[2]; Arne Astrup (Denmark)[5]; Ulla Feldt-Rasmussen (Denmark)[1]

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Background and Objective: Hypothalamic obesity results in severe weight-gain and increased risk of cardiovascular and metabolic mortality. Currently, there are no approved or effective pharmacological treatments and conventional weight management remains largely ineffective. This trial investigated safety and efficacy of tesomet (0.5 mg tesofensine and 50 mg metoprolol) in hypopituitary patients with hypothalamic obesity.

Methods: Twenty-one (16 females) hypopituitary patients with hypothalamic obesity were randomized to tesomet or placebo (2:1) for 24 weeks (NCT03845075). Subjects also received diet and lifestyle counselling. Primary endpoint was safety evaluated by change in vitals and adverse events. Secondary endpoints included change in anthropometric measures, appetite-score and pituitary replacements.
The mean (SD) age of subjects was 46 (14.6) years and 90% had a BMI ≥30 kg/m^2. Almost half had a history of craniopharyngioma, 86% had undergone pituitary/hypothalamic surgery, 52% irradiation. All received one or more anterior pituitary hormone replacements; 52% had diabetes insipidus.
Results: Four subjects, two in each group, discontinued treatment. In the treatment arm discontinuation was secondary to anxiety (n=1) or dry mouth (n=1); both improved after drug discontinuation. Adverse events were mild (58%) and included sleep disturbances (62%), dry mouth (46%), dizziness (46%) and headache (38%), known side-effects of tesofensine or metoprolol. No significant differences in heart rate or blood pressure were observed between the two groups. 18/21 subjects completed the study, one without investigational treatment.
At week 24, compared to placebo (weight loss -0.3%), tesomet treatment resulted in additional mean ([95CI], *p*-value) weight loss of -6.3% ([-11.3%; -1.3%], *p*=0.017); increase in the proportion of patients achieving >5% reduction in body weight (tesomet 8; placebo 1, OR 11.2 [1.0; 120.4], *p*=0.046); reduction in waist circumference of -5.0% ([-10.1%; 0.1%], *p*=0.052). Treatment resulted in transient numerical improvements in subjective appetite score over placebo.
Most subjects (62%) had their levothyroxine reduced; adjustments in pituitary replacement and diabetic medications were otherwise few and did not differ significantly from baseline. Mean (SD) change in levothyroxine daily dose from baseline was -6.6% (6.1) and -6.4% (9.1) in tesomet and placebo, respectively. In both groups, change in levothyroxine correlated with weight-loss at time of adjustment (r^2=0.37, *p*=0.006).
Conclusion: Tesomet was generally well tolerated, did not affect heart rate or blood pressure, resulted in transient appetite-suppression, significant reductions in body weight and waist circumference compared to placebo in this cohort of hypopituitary patients with hypothalamic obesity. Weight-loss necessitated reductions in levothyroxine dose in most subjects.

OC-03 - PITUITARY ADENOMAS IN THE ELDERLY: MORE OF THE SAME? – COMPARATIVE ANALYSIS BY AGE GROUP

Patrícia Rosinha (Portugal)[3]; Liliana Fonseca (Portugal)[1]; Ana Lopes (Portugal)[1]; Vânia Benido (Portugal)[1]; Sílvia Monteiro (Portugal)[1]; Catarina Chaves (Portugal)[4]; Cláudia Amaral (Portugal)[1]; Isabel Ribeiro (Portugal)[2]; Helena Cardoso (Portugal)[1]

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Aim: This study was conceived to compare clinical and tumor features between patients with pituitary adenomas from different age groups (younger and older adults), seeking to name its particularities in the elderly.
Background and Methods: The increase in life expectancy along with technological advances have translated into an increasing number of pituitary adenomas diagnosed from the age of 65. This age group is often characterized by having multiple co-morbidities, increasing the risk of symptom overlap with endocrine dysfunction and perioperative complications.
We performed a retrospective observational study including patients with diagnosis of pituitary adenoma in adulthood and follow-up at our institution, divided in 2 groups: younger adults (YA), 18-64 years, and older adults (OA), ≥65 years.
For statistical analysis, we used Pearson qui-square test and Fisher exact test to evaluate differences between groups and a *p*-value <0.05 was considered statistically significant (SPSS v.20).
Results: A total of 401 patients met the inclusion criteria: 327 (81.5%) from YA and 74 (18.5%) from OA group. There was a preponderance of female patients in both groups (61.5% in YA and 62.2% in OA, *p*=0.912). Hormone-secreting effects were more common in YA (41.9% *vs* 12.2%, *p*<0.001) and mass effects were more frequently observed in OA (52.7% *vs* 41.6%, *p*=0.070). The prevalence of hypertension and diabetes was significantly higher in OA group, respectively 43.2% (*vs* 23.9%, *p*=0.002) and 24.3% (*vs* 12.5%, *p*=0.011). Giant adenomas were more common from the age of 65 (9.4% *vs* 0%, *p*=0.352), however, there were no significant differences in terms of invasiveness and, with regard to extension, only suprasellar was significantly higher in OA (83.5% *vs* 30.0%, *p*=0.025). Pituitary apoplexy and secondary hormonal deficits were more frequent in OA group, despite not statistically significant difference. A larger proportion of nonfunctioning adenomas and prolactinomas was found, respectively, in OA (48.6% *vs* 26.6%, *p*<0.001) and YA (38.5% *vs* 23.0%, *p*=0.012).
OA patients with prolactin-secreting adenomas had more frequently cavernous sinus invasion (47.0% *vs* 22.2%, *p*=0.026).
Conclusion: OA pituitary adenomas clinically differ from the younger: tend to present more frequently by mass-effect symptoms and apoplexy, have concomitant secondary hormonal deficits, be larger in size without mandatory increase in invasiveness. These features are probably related with the difficulty in recognizing endocrine dysfunction in the elderly, leading to a delayed diagnosis and, this way, a riskier clinical picture.

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OC-04 - CLINICAL, CELLULAR, AND MOLECULAR EVIDENCE OF THE ADDITIVE ANTITUMOR EFFECTS OF BIGUANIDES AND STATINS COMBINATION IN PROSTATE CANCER

Antonio J. Montero-Hidalgo (Spain)[1,2,3,4]; Juan M. Jiménez-Vacas (Spain)[1,2,3,4]; Vicente Herrero-Aguayo (Spain)[1,2,3,4]; Prudencio Sáez-Martínez (Spain)[1,2,3,4]; Enrique Gómez-Gómez (Spain)[1,3,4,5]; Antonio J. León-González (Spain)[1,2,3,4]; Elena M. Yubero-Serrano (Spain)[1,3,4,6]; María J. Requena-Tapia (Spain)[1,3,5]; Miguel López (Spain)[4,7]; Justo P. Castaño (Spain)[1,2,3,4]; Manuel D. Gahete (Spain)[1,2,3,4]; Raúl M. Luque (Spain)[1,2,3,4]

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Prostate cancer (PCa) is the most common endocrine-dependent tumor among men in developed countries and represents one of the leading causes of cancer-related death within this population. Unfortunately, current medical treatments fail to prevent PCa progression in a high percentage of cases. Therefore, the discovery and establishment of new therapeutic approaches to tackle PCa are urgently needed. An emerging approach against several tumor types is based on repositioning already approved drugs for other pathologies. In this scenario, biguanides and statins have emerged as antitumour agents for several endocrine-related cancers. However, it is still controversial the precise molecular mechanisms underlying these antitumour effects in PCa. Thus, we aimed to evaluate: 1) the putative in vivo association between metformin and/or statins treatment and key tumour and clinical parameters, and 2) the direct effects of different biguanides (metformin, buformin, and phenformin), statins (atorvastatin, simvastatin, and lovastatin), and their combination, on key functional endpoints and the associated signalling mechanisms underlying these effects in PCa cells. To that end, we analysed an exploratory/observational retrospective cohort of patients with PCa (n=75), and carried out functional (cell proliferation/migration and tumorsphere formation) and mechanistic (qPCR and Western Blot) assays using normal and tumour prostate cells [normal (RWPE-1 cell-line and primary prostate cell-cultures); tumour (LNCaP, 22Rv1, PC-3, and DU145 cell-lines)]. Interestingly, the *in vivo* combination of metformin and any statin was associated with lower Gleason score and longer biochemical recurrence-free survival. Additionally, biguanides and statins exerted strong antitumour actions (i.e. inhibition of cell proliferation/migration and tumorspheres formation) on PCa cells, and their combination further decreased, in an additive manner, these functional parameters compared with the individual treatments. These actions were mediated through the modulation of key oncogenic and metabolic signalling pathways (i.e. androgen-receptor, mTOR, AMPK, AKT, ERK) and molecular mediators (MKI67, c-MYC, androgen-receptor, and cell-cycle inhibitors). Altogether, our results reveal that biguanides and statins significantly reduced tumour aggressiveness in PCa, being this effect more potent (*in vivo* and *in vitro*) when both compounds are combined. Therefore, given the demonstrated clinical safety of biguanides and statins, our results suggest a potential therapeutic role of these compounds, especially their combination, for the treatment of PCa.

Fundings:
ISCIII (PI16-00264), MINECO/MECD (PID2019-105564RB-I00, FPU18-02485), CIBERobn.

OC-05 - GASTROINTESTINAL ADVERSE EVENTS WITH ORAL OCTREOTIDE CAPSULES: SAFETY RESULTS FROM THE PHASE 3 CHIASMA OPTIMAL STUDY

Artak Labadzhyan (United States of America)[1]; Susan Leanne Samson (United States of America)[2]; Lisa B Nachtigall (United States of America)[3]; Maria Fleseriu (United States of America)[4]; Mark E Molitch (United States of America)[5]; William Henry Ludlam (United States of America)[6]; Gary Patou (United States of America)[7]; Asi Haviv (United States of America)[6]; Agata Baldys Waligorska (Poland)[8]; Nienke Biermasz (Netherlands)[9]; Laurence Kennedy (United States of America)[10]; Christian Joseph Strasburger (Germany)[11]; Shlomo Melmed (Germany)[1]

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Background & Methods: Injectable somatostatin receptor ligands (SRLs) are the mainstay of medical treatment in acromegaly. GI AEs are common disease-related AEs and also the most common AEs associated with SRL treatment. In a study of 105 patients, 72% experienced GI AEs lasting an average of 10 days after injection. SRL-associated AEs interfered with daily and leisure activities in >80% of patients.[1,2] Oral octreotide capsules (OOC), recently approved in the US, are a treatment option for patients with acromegaly previously responding to injections. Safety and efficacy of OOC were established in the phase 3 CHIASMA OPTIMAL pivotal study.[3] Safety data derived from 56 patients randomized to OOC or placebo during the DPC period were evaluated for OOC compared to placebo, enabling differentiating between disease-related GI AEs and SRL–related AEs.
Results: GI disorders were the most common AEs reported in both groups (OOC, 67.9% of patients; placebo, 60.7% of patients), and were the most common AE assessed as study drug related. GI AEs occurring more often in the OOC group included diarrhea, nausea, abdominal discomfort, vomiting, and dyspepsia, while constipation, upper abdominal pain, and flatulence occurred more often in the placebo group. All GI treatment-emergent AEs (TEAEs) in the OOC group were mild or moderate, with a median onset of 68 days (range, 1–214) and a median duration of 8 days. Two thirds of GI AEs in the OOC group occurred within the first 120 days of the study. In the placebo group, median AE time of onset was 30 days (range, 1–233), and median duration was 17 days. In the OOC group, 1 patient discontinued study drug owing to AEs including GI discomfort, dyspepsia, nausea, and vomiting.
Conclusion: The safety profile of OOC was similar to injectable SRLs, with GI AEs being most commonly encountered. GI AEs more prevalent in the placebo group including constipation, upper abdominal pain, and flatulence may have been disease related or related to the withdrawal of long-acting SRLs. Safety results from

the CHIASMA OPTIMAL study indicate that GI AEs resolved on average within about a week, and AE frequency reduced with time, unlike GI AEs associated with long-acting SRLs, which tend to recur in patients for a few days after injection.[3]

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OC-06 - DYSREGULATION OF SPLICING MACHINERY IS ASSOCIATED WITH TUMOR DEVELOPMENT AND PROGNOSIS IN ADAMANTINOMATOUS CRANIOPHARYNGIOMAS

Antonio C. Fuentes-Fayos (Spain)[1,2,3,4]; Teresa Sánchez-Medianero (Spain)[1,2,5]; David A. Cano (Spain)[6]; Antonio J. Martínez-Ortega (Spain)[6]; John R. Apps (United Kingdom)[7]; Georg Otto (United Kingdom)[7]; Álvaro Toledano-Delgado (Spain)[1,2,8]; Elena Dios (Spain)[6]; Eva Venegas-Moreno (Spain)[6]; Eugenio Cárdenas (Spain)[9]; Juan P. Martínez-Barbera (United Kingdom)[7]; Rosa M. Ortega-Salas (Spain)[1,2,5]; Justo P. Castaño (Spain)[1,2,3,4]; Alfonso Soto-Moreno (Spain)[6]; Raúl M. Luque (Spain)[1,2,3,4]

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Craniopharyngiomas are relatively benign neoplasms that typically arise in the sellar/suprasellar region. There are two histological subtypes, adamantinomatous (ACPs) and papillary (PCPs), which differ in prognosis and morphology. They are more prevalent in childhood, adolescence, and adults <50 years, and, commonly, are usually diagnosed after being associated with serious comorbidities, when the development of the tumor is already advanced. To date, first-line therapy is usually surgery, but frequently the resection is not complete, causing high rates of recurrence. Therefore, the identification of new diagnostic and prognostic biomarkers as well as therapeutic tools to improve the management of patient with craniopharyngiomas is necessary. In recent years, a growing evidence indicates that the aberrant presence of splicing variants (SVs) together with defects in the splicing process are frequent in tumor pathologies, leading to the appearance of altered spliceosome components (SCs) and splicing factor (SFs), which are associated to the development, progression and aggressiveness of various cancer types. Thus, the aim of this study was to establish the expression profile of key splicing machinery components [major and minor spliceosome machinery (n=13/4, respectively) and 28 relevant SFs] in ACPs (primary and recurrent tumors; n=36) compared with control samples [normal pituitary glands (NPs, n=11)] using a microfluidic qPCR-array, to explore their potential dysregulation and to identify specific components of this machinery that could serve as diagnostic and/or prognostic biomarkers as well as therapeutic targets for ACPs. Expression of splicing machinery components and SFs were drastically altered in ACPs vs. NPs, and, also when primary vs. recurrent ACPs were compared. Bioinformatic analyses identified *RAVER1*, *RBM22*, *FBP11* and *PRPF8* as the most discriminating diagnostic/prognostic factors of ACPs being corroborated in human ACP and PCP external cohorts. Furthermore, some of these components were associated with key clinical parameters suggesting a potential patho-physiological role in ACPs. Finally, an *in vitro* modulation of *RAVER1* and *PRPF8* expression (the most relevant SCs identified) and the treatment with a splicing machinery inhibitor (pladienolide-B) in primary ACP-derived cell cultures revealed a critical role of the splicing machinery in the pathophysiology of craniopharyngiomas. Likewise, *PRPF8* overexpression was associated with the presence of some splicing variants that could play a critical role in ACP tumorigenesis. Altogether, the expression of key splicing machinery components and SFs is dysregulated in craniopharyngiomas, which provides an original approach to identify novel diagnostic and/or prognostic biomarkers and new targets with therapeutic potential in craniopharyngiomas.

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OC-07 - SPLICING DYSREGULATION IN PANCREATIC NEUROENDOCRINE TUMORS: CONTRIBUTION OF CELF4 SPLICING FACTOR TO PANNET AGGRESSIVENESS

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Dysregulation of the alternative splicing process is emerging as a novel cancer hallmark, due to its contribution to multiple dysfunctions in tumor cells. In particular, inappropriate functioning of the splicing machinery (spliceosome and splicing factors) can generate oncogenic splicing variants in tumors. In previous studies, we showed that overexpression of aberrant alternative splicing variants of somatostatin receptor 5 (SST_5TMD4) and ghrelin (In1-ghrelin) are overexpressed and directly associated to malignant features in pancreatic neuroendocrine tumors (PanNETs). Subsequently, we uncovered a profound dysregulation of the splicing machinery in PanNETs. This study focused in one of the most altered splicing factors identified, *CELF4*, by assessing its features, regulation and functional role in PanNETs. *CELF4* expression levels were determined by qPCR in a cohort of 20 PanNETs (47% G1, 47% G2 and 6% G3), in paired tumor and corresponding non-tumoral adjacent tissue, used as reference. Additionally, two PanNET model cell lines, BON-1 and QGP-1, served to explore *CELF4* function *in vitro*: cell viability was assessed using Alamar Blue assay, and gene expression and protein levels of key signaling components were determined through qPCR and Western blot, respectively. Expression levels of *CELF4* were found to be drastically upregulated in PanNETs, where they associated with relevant malignancy features, such as metastasis. Importantly, functional *in vitro CELF4* modulation revealed that induction of gene silencing and overexpression evoked, respectively, a reduction and a stimulation in cell proliferation. Moreover, *CELF4* silencing altered key signaling pathways and hampered the response of both cell lines to everolimus treatment, thereby suggesting that *CELF4* may play a role in tumor cell aggressiveness and that it could be a suitable actionable tool in PanNETs. Our results demonstrate that the splicing factor CELF4 is severely dysregulated in PanNETs, where it could influence tumor development and aggressiveness. These findings provide original evidence inviting to further explore this splicing factor as novel a potential diagnostic marker and treatment target in PanNETs.

OC-08 - THE X-LINKED ACROGIGANTISM-ASSOCIATED GENE GPR101 REGULATES EARLY EMBRYONIC DEVELOPMENT AND GROWTH IN ZEBRAFISH

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Background: X-linked acrogigantism is a condition of early childhood-onset pituitary gigantism caused by duplications of *GPR101*, a gene predominantly expressed in the brain.
Aim: To elucidate *GPR101*'s role during embryonic development and its effects on body growth.
Methods: mRNAs encoding *gpr101* and *GPR101* were microinjected into wild-type (WT) zebrafish embryos. gpr101 knockouts (KOs) were generated by CRISPR-Cas9. Maternal-zygotic *gpr101* KO (MZ*gpr101*) embryos were obtained by in-crossing homozygous mutant parents. Growth was monitored until 9 weeks post-fertilization (wpf). mRNA expression was measured by qPCR. Development of MZ*gpr101* embryos from fertilization to 24 hpf was recorded by time-lapse microscopy. Morphometric analysis of MZ*gpr101* brains was done by staining 6 dpf larvae with lysotracker and imaging with a confocal microscope. RNA-Seq analysis was performed in embryos with both loss and ectopic activation of *gpr101*.
Results: Transient expression of both orthologues caused early axis patterning defects that manifested as cyclopean and dorsalizing phenotypes, but did not affect growth. Pathway analysis at gastrulation's onset revealed an enrichment for gene sets related to early patterning, morphogenetic processes, and cell fate commitment. Several upregulated genes are involved in the formation of the neural tube or are expressed in the brain and pituitary.
gpr101 KOs showed a significant decrease in standard length and body weight (both $p<0.0001$) throughout juvenile development. Surprisingly, the smaller size was not accompanied by significant differences in the expression of hypothalamic or pituitary hormones. To characterize the contribution of both maternally and zygotically supplied *gpr101*, we investigated MZ*gpr101*. The majority of embryos did not undergo cleavage, indicating very low fertility. The surviving mutants were consistently smaller than WT controls at all time points examined ($p<0.0001$), an effect 2-fold greater in magnitude compared to the KOs. We observed significant decreases in *igf2a* ($p=0.0096$) and *sst1.1* ($p=0.0015$) expression and a tendency for *gh1* ($p=0.0669$), indicating a perturbed growth axis. A morphometric analysis of the brains revealed an enlarged hypothalamic-pituitary unit ($p<0.01$).
Transcriptomic studies in eggs devoid of *gpr101* indicated that the deposition of several maternal factors was altered. An enrichment for gene sets involved in cell morphogenesis, cell adhesion, and drug/ion transport was detected in MZ*gpr101* embryos entering gastrulation, a finding consistent with the observed perturbed cell movements.
Conclusion: We provide the first *in vivo* evidence that *gpr101* regulates embryonic growth. We uncovered essential roles for this gene for fertilization competence and for viable morphogenesis during the blastula/gastrula stages. These defects later manifested as brain anomalies.

OC-09 - GERMINAL DEFECTS OF SDHX GENES IN PATIENTS WITH ISOLATED PITUITARY ADENOMA

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Background: The '3PAs' syndrome, associating pituitary adenoma (PA) and pheochromocytoma/paraganglioma (PPGL), is sometimes associated with mutations in PPGL-predisposing genes, such as SDHx or MAX. In '3PAs' syndrome, PAs can occur before PPGL, suggesting a new gateway into SDHx/MAX-related diseases.
Objective: To determine the SDHx/MAX mutation prevalence in patients with isolated PAs and characterize PAs of patients with SDHx/MAX mutations.
Design: Genes involved in PAs (AIP/MEN1/CDKN1B) or PPGLs (SDHx/MAX) were sequenced in patients with isolated PAs. We then conducted a review of cases of PA in the setting of '3PAs' syndrome.
Results: A total of 263 patients were recruited. Seven (likely) pathogenic variants were found in AIP, two in MEN1, two in SDHA, and one in SDHC. The prevalence of SDHx mutations reached 1.1% (3/263). Of 31 reported patients with PAs harboring SDHx/MAX mutations (28 published cases and 3 cases reported here), 6/31 (19%) developed PA before PPGL and 8/31 (26%) had isolated PA. The age of onset was later than in patients with AIP/MEN1 mutations. PAs were mainly macroprolactinomas and showed intracytoplasmic vacuoles seen on histopathology.
Conclusion: We discovered SDHx mutations in patients bearing PA who had no familial or personal history of PPGL. However, the question of incidental association remains unresolved and data to determine the benefit of SDHx/MAX screening in these patients are lacking. We recommend that patients with isolated PA should be carefully examined for a family history of PPGLs. A family history of PPGL, as well as the presence of intracytoplasmic vacuoles in PA, requires SDHx/MAX genetic testing of patients.

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OC-10 - TREATMENT OF ISOLATED IDIOPATHIC GH DEFICIENCY IN CHILDREN AND THYROID FUNCTION: IS THE NEED FOR LEVOTHYROXINE A CONCERN IN LONG-TERM THERAPY?

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Background: Treatment with GH alters thyroid hormones metabolism. Recombinant human growth hormone (rhGH) replacement therapy seems to be able to induce hypothyroidism, but it is a controversial issue. Our aim was to assess the effects of rhGH replacement therapy on thyroid function in a group of euthyroid children with isolated idiopathic growth hormone deficiency (GHD).
Methods: Retrospective analysis of the medical files of 56 children with isolated idiopathic GHD treated with rhGH for at least 1 year. Auxological (weight SDS, height SDS, growth velocity [GV] SDS) and biochemical (free thyroxine [FT4], TSH, and IGF-1 parameters were recorded before, during, and after treatment with rhGH.
Results: FT4 and TSH levels decreased significantly during rhGH therapy in children with isolated idiopathic GHD. Twenty-one percent (n=12) of the children developed hypothyroidism, about 4 years (mean 46.9 ± 38.0 months) after initiation of rhGH, and lower baseline FT4 levels appears to predict the need for levothyroxine (LT4) (OR=0.8, CI 0.592-0.983; *p*=0.036). Hypothyroidism was reversible after interruption of rhGH, except in one patient; FT4 levels returned to baseline in the first year after completing the treatment. Final height SDS of the children who developed hypothyroidism was not different from their counterparts without hypothyroidism (-1.24 [-1.52 to -1.10] *vs* -1.13 [-1.78 to -0.74], *p*=1.000). Predicted adult height (PAH) SDS was similar in both LT4 supplemented (n=7; final Ht SDS -1.16 [-1.31 to -1.10] *vs* PAH -1.00 [-1.42 to -0.48]; *p*=0.398) and not supplemented patients (n=25; final Ht SDS -1.46 [-1.83 to -0.78] *vs* PAH SDS -0.88 [-1.35 to -0.56]; *p*=0.074).

Table 3. Association between baseline clinical, auxological and biochemical parameters and time to hypothyroidism onset (n=56)

	Univariate analysis		Multivariate analysis*	
	HR [95% CI]	***p***	**HR [95% CI]**	***p***
Age, years	0.99 [0.82, 1.20]	0.920	-	-
Feminine sex	0.80 [0.24, 2.69]	0.720	0.80 [0.24, 2.69]	0.719
Puberty	0.88 [0.33, 2.32]	0.797	0.89 [0.35, 2.72]	0.813
Weight SDS	1.41 [0.69, 2.88]	0.347	1.56 [0.76, 3.23]	0.226
Height SDS	1.23 [0.66, 2.31]	0.513	1.29 [0.66, 2.51]	0.452
BMI SDS	1.07 [0.59, 1.95]	0.821	1.08 [0.59, 1.98]	0.803
GV SDS	1.04 [0.71, 1.52]	0.841	1.04 [0.71, 1.54]	0.831
IGF-1 SDS	1.11 [0.72, 1.70]	0.613	1.13 [0.72, 1.77]	0.598
FT4 (ng/dL)	0.001 [0.00, 0.23]	0.014	0.001 [0.00, 0.25]	0.016
TSH (µU/L)	1.12 [0.65, 1.91]	0.687	1.11 [0.65, 1.92]	0.701
GH lower peak (ng/mL)	1.06 [0.74, 1.53]	0.748	1.07 [0.72, 1.56]	0.732
rhGH dose**	0.19 [0.03, 1.25]	0.084	0.19 [0.03, 1.28]	0.090

BMI – body mass index; FT4 - free thyroxine; GH – growth hormone; GV – growth velocity; HR – hazard ratio; IGF-1 -insulin-like growth factor-1; PAH - predicted adult height; SDS – standard deviation scores; TSH - thyroid-stimulating hormone
* data adjusted for age; **rhGH dose in mg/kg/day was multiplied by a factor of 100

Table 4. Comparison of thyroid function of patients before and during rhGH treatment (n=52)

	Before therapy	3-6 months therapy	*p**	12-18 months therapy	*p**	24-30 months therapy	*p**
FT4 (ng/dL)	1.1 ± 1.14	1.0 ± 0.12	0.005	1.0 ± 0.14	< 0.001	1.0 ± 0.15	0.001
TSH (µU/L)	2.6 ± 1.06	1.9 ± 0.87	< 0.001	1.7 ± 0.66	< 0.001	1.7 ± 0.88	< 0.001

FT4 - free thyroxine; TSH - thyroid-stimulating hormone;
* *vs* pre-therapy values

Table 6. Comparison of clinical, auxological and biochemical parameters before rhGH treatment according to LT4 supplementation (n=56). *Values are shown as mean ± standard deviation or as median [95% confidence interval].*

	LT4 supplementation (n=12)	No LT4 supplementation (n=44)	*p**
Age, years	8.3 ± 3.26	9.8 ± 3.23	0.177
Sex, %			0.525
Feminine	33.3%	45.5%	
Masculine	66.7%	54.5%	
Pubertal state			1.000
Prepubertal	85.7%	77.8%	
Pubertal	14.3%	22.2%	
Weight SDS	-1.7 ± 1.30	-1.9 ± 1.11	0.715
Height SDS	-2.6 [-3.07 to -2.29]	-2.6 [-3.14 to -2.36]	0.792
BMI SDS	-0.1 ± 0.87	-0.1 ± 1.21	0.864
GV SDS	-2.2 ± 1.70	-2.1 ± 1.91	0.904
IGF-1 SDS	-1.1 ± 1.31	-1.2 ± 1.24	0.866
FT4 (ng/dL)	1.0 ± 0.07	1.1 ± 0.14	**0.002**
TSH (µU/L)	2.8 ± 1.23	2.5 ± 0.99	0.312
GH lower peak (ng/mL)	3.5 ± 2.24	3.3 ± 1.79	0.726
rhGH dose (mg/kg/day)	0.030 ± 0.002	0.032 ± 0.004	**0.042**

BMI – body mass index; FT4 - free thyroxine; GH – growth hormone; GV – growth velocity; IGF-1 -insulin-like growth factor-1; LT4 – levothyroxine; PAH - predicted adult height; SDS – standard deviation scores; TSH - thyroid-stimulating hormone.

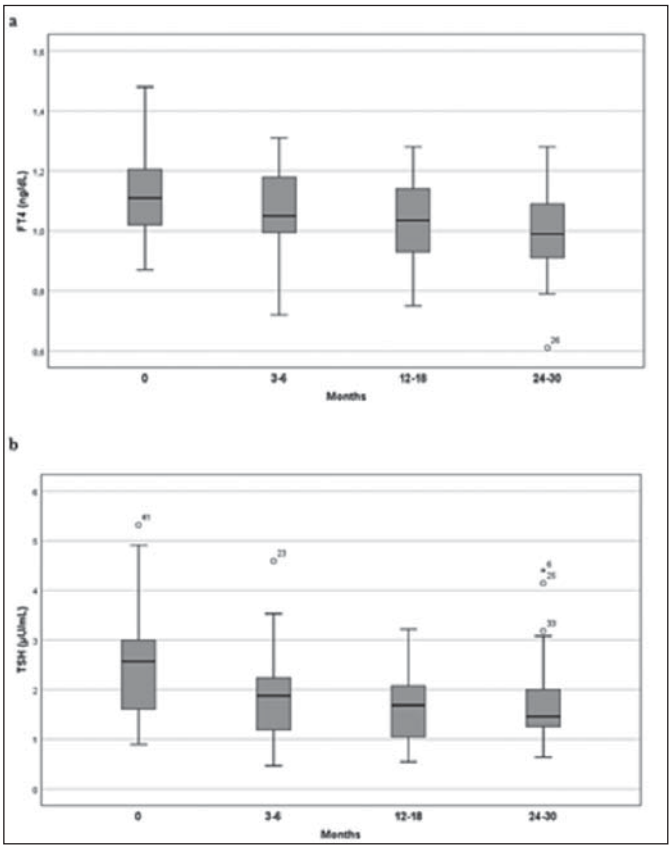

Figure 1. Boxplot of serum FT4 levels (a) and TSH levels (b) before and during rhGH treatment (n=52).

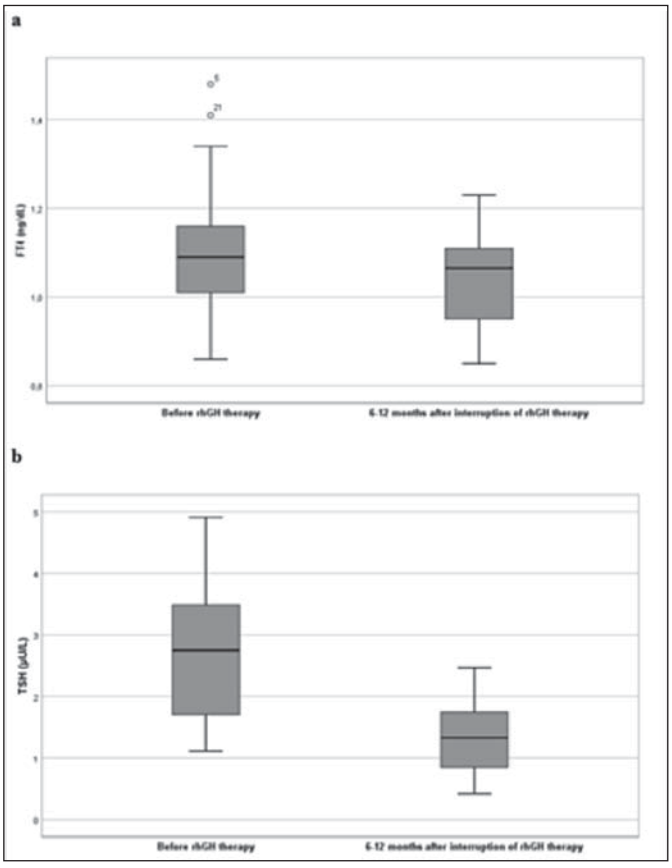

Figure 2. Boxplot of serum FT4 levels (a) and TSH levels (b) before initiating and 6-12 months after interruption of rhGH treatment (n=34).

Conclusion: A significant number of patients with isolated idiopathic GHD develop transitory need for LT4 during GH treatment. Adequate LT4 supplementation allows patients to achieve their PAH, similarly to those who do not need hormonal replacement.

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CONGRESS ABSTRACTS

E-Posters

EP-01 - PANHYPOPITUITARISM: ARE WE MISSING IT? A 'CENTRAL' PROBLEM IN METASTATIC MELANOMA: IMMUNOTHERAPY INDUCED HYPOPHYSITIS

Padmini Giri (United States of America)[1]; Laith Al-Janabi (United States of America)[1]; Verisha Khanam (United States of America)[1]; Sourabh Fnu (United States of America)[1]; Ameer Khan (United States of America)[1]; Ankita Gandhi (United States of America)[1]; Manishkumar Patel (United States of America)[1]

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Introduction: Hypopituitarism is a result of decreased hormonal secretions from the pituitary. Causes for such an occurrence are broad and include infections, tumors, radiation therapy, stroke, etc. Uncommon causes for hypophysitis include medications. One such medication includes nivolumab, an immune checkpoint inhibitor, targeting the PD-1 protein, causing downregulation of T-cell response and increasing antitumor activity by immune system. Although considerable clinical benefits have been established by the use of these therapies, they are also linked with a broad spectrum of dangerous side-effects including immune-related adverse events due to increased activation of the immune system. These immune-related-adverse-effects, can vary from mild to severe and can be seen in the form of gastrointestinal, dermatological, endocrine features. Here we present a case of a patient who presented with an assortment of symptoms, likely induced by nivolumab.
Case Report: 51-year-old Caucasian female with metastatic melanoma receiving nivolumab (8 sessions) presented with fever, generalized rash, diarrhea, lethargy, hypoxia (no home oxygen) with hypotension. She was received to the ICU in Septic shock with no improvement of her BP after 7-liter fluid boluses; at the time viral source of infection was suspected. AM cortisol was 1.0 and TSH and T4 were both low, suggestive of hypopituitarism. The patient's BP improved with just one dose of IV hydrocortisone. It is suspected that her chemotherapy treatment is the cause for these symptoms as the patient had a recent PET scan done which was only positive for spread to abdominal lymph-nodes.
Disccusion: Nivolumab has been recently approved by the FDA for unresectable melanoma. The approval of newer medications and broaden use of such therapies although has many clinical benefits, can be associated with adverse effects, in patients who are already trying to fight a life-threatening ailment. Immune mediated events with Nivolumab occurs accounts for ≤ 12% of adverse effects. Anti-PD-1-associated hypophysitis is a remarkably sporadic phenomenon, occurring in either <1% of patients in multiple studies. The presentation in which our patient presented was not typical. It is like a mind-block for healthcare professionals when an immunosuppressed patient on chemo for a metastatic malignancy presents with septic shock and hypoxia, to automatically look for an underlying infection or pulmonary embolism. Healthcare professionals are unfamiliar with these rare consequences of these therapies. To conclude, nivolumab induced hypophysitis is exceptionally rare with serious endocrinological and hemodynamic penalties. It is critical for practitioners and patients to be cognizant of these complications throughout the already tough journey of cancer-therapy.

EP-02 - A CASE OF FAMILIAL ACROMEGALY AND BILATERAL ASYNCHRONOUS PHEOCHROMOCYTOMAS DUE TO A MAX MUTATION

Elizaveta Mamedova (Russian Federation)[1]; Evgeny Vasilyev (Russian Federation)[1]; Vasily Petrov (Russian Federation)[1]; Svetlana Buryakina (Russian Federation)[1]; Anatoly Tiulpakov (Russian Federation)1; Zhanna Belaya (Russian Federation)[1]

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Introduction: Approximately five patients with a combination of pituitary adenoma (PA) and bilateral synchronous or asynchronous pheochromocytomas with *MAX* mutations have been described to date,[1-3] thus making each novel case of particular importance.
Background & Methods: A 38 y.o. patient presented with complaints of high blood pressure. At the age of 21 she was diagnosed with pheochromocytoma (she was investigated due to hypertension up to 180/100 mm Hg, and CT revealed the right adrenal mass 6.1x4.4x4.2 cm; vanillyl mandelic acid in urine was elevated 19.7 mg/24h (0-7)). Right adrenalectomy was performed and diagnosis of pheochromocytoma was histologically confirmed. At the age of 25 amenorrhea and galactorrhea developed. PRL level was elevated (>7000 IU/mL) and MRI revealed a PA 14x24x17 mm. After prescription of cabergoline 1.5 mg/weekly her PRL level normalized and PA decreased in size. At the age of 33 cabergoline was withdrawn due to persistent PRL normalization. At admission, symptoms of acromegaly were noticed (facial and acral enlargement). Her laboratory results were as follows: IGF-1 451.4 ng/mL (82-283), PRL 489.1 IU\mL (64-395), urine epinephrine 665.7 µg/24h (25-312), urine norepinephrine 1619.1 µg/24h (35-445). MRI revealed a PA 22x8x14.8 mm. CT revealed three nodules in the left adrenal 21x22x23 mm, 24x14x19 mm and 24x22x24 mm, with density of +44HU. The patient's deceased father had pronounced acromegaly features on the photographs. NGS of *MEN1*, *AIP*, *CDKIs* and *SDHx* revealed no abnormalities and in order to reveal genetic background whole-exome sequencing (NextSeq550, Illumina, USA) was performed.
Results: A nonsense mutation in exon 4 of *MAX* gene (NM_002382) c.223C>T (p.R75X) was identified. This mutation

has been previously described in patients with familial bilateral pheochromocytomas,4 but not in patients with combined PA and pheochromocytoma.
Conclusion: Here we describe a female patient with familial acromegaly (PA, possibly of mixed GH/PRL secretion) and bilateral asynchronous pheochromocytomas with a nonsense *MAX* mutation. The role of *MAX* in familial pheochromocytomas/paragangliomas has been investigated, though its role in development of familial pituitary adenomas remains to be established.

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EP-03 - COVID-19 INFECTION IN PATIENTS WITH CUSHING'S SYNDROME: A REPORT OF THREE CASES

Zhanna Belaya (Russian Federation)[1]; Olga Golounina (Russian Federation)[2]; Evgeniya Pashkova (Russian Federation)[3]; Victor Kalashnikov (Russian Federation)[1]; Natalya Tarbaeva (Russian Federation)[1]; Maksim Gorohov (Russian Federation)[1]; Elena Przhialkovskaya (Russian Federation)[1]; Dmitriy Belcevich (Russian Federation)[1]

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Background: Coronavirus disease-19 (COVID-19) is a novel viral pandemic disease caused by SARS-CoV-2.
Objective: To analyze the specific clinical presentation and complications of patients with Cushing's syndrome (CS) affected by novel COVID-19. We report three distinct cases of CS with confirmed COVID-19.
Material and methods: Plasma levels of ACTH (reference range: morning 7.2–63.3 pg/mL), late-night serum cortisol (64–327 nmol/L), late-night salivary cortisol (LNSC) (0.5–9.6 nmol/L) by ECLIA Cobas 601; 24hUFC (100–379 nmol/L) were measured in all subjects. Two nasopharyngeal and oropharyngeal throat swab samples were collected from each patient and tested for SARS-CoV-2 using RT-PCR.
Results: Patient 1, a 71-year-old woman was diagnosed with ACTH dependent hypercortisolism in April 2020 (late-night serum cortisol >1750 nmol/L, LNSC 908.6 nmol/L, ACTH 445.8 pg/mL) with no detectable tumor. Life-threatening complications (anemia (Hb 92 g/L (112–153 g/L), hypokalemia (potassium 2.5 mmol/L (3.5–5.1 mmol/L), hypoalbuminemia (albumin 27 g/L (34–48 g/L), kidney failure (GFR – 21 mL/min/1.73 m^2) were partially compensated in order to prepare the patient for bilateral adrenalectomy. However, 15 days after hospitalization she developed dyspnea. Her respiratory status rapidly deteriorated during the next 4 days due to COVID-19 pneumonia (degree of lungs involvement 80%). This patient died 7 days after COVID-19 was confirmed. The official cause of death was COVID-19 complicated with bilateral polysegmantal haemorrhagic pneumonia and ARDS.
Patient 2, a 38-year-old woman, who underwent 3 transsphenoidal neurosurgeries between 2015 and 2020. She never had remission of Cushing's disease (late-night serum cortisol 581.3 nmol/L, 24hUFC 959.7 nmol/L ACTH 74.42 pg/mL). The patientwas hospitalized with progression of dyspnea, cough, fever (39.3°C), chest pain. Oxygen therapy, antibiotics, symptomatic treatments were required. Her condition resolved on day 24 after admission. She was discharged from a hospital without symptoms.
Patient 3, a 66-year-old woman, with a 4-year medical history of active Cushing's disease without remission after a neurosurgery (ACTH 25.67 pg/mL, late-night serum cortisol 603.4 nmol/L, LNSC 10.03 nmol/L), hypertension and type 2 DM. She was tested positive for COVID-19 in a routine screening. CT scan showed the typical signs specific to COVID-19 pneumonia (degree of lungs involvement 4%). Her vital parameters were stable, with no fever, cough or difficulty breathing. The patient was hospitalized in order to prevent possible complications. She made a full recovery after 10 days, remaining asymptomatic.
Conclusion: The clinical course of COVID-19 is difficult to predict in patients with CS. However, it seems that COVID-19 pneumonia may progress rapidly in severe cases of CS.

EP-04 - THE HISTOLOGICAL STRUCTURE OF PATIENTS WITH NONFUNCTIONAL PITUITARY GIANT ADENOMAS (NFPA)

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Aim of the Research: To study the histological structure of nonfunctional pituitary giant adenomas (NFPA).
Material and Methods: We observed 21 patients with giant NFPA, among them 10 male and 11 female, mean age 37.8. All patients were undergone surgical treatment by transsphenoidal access in Center of Endocrinology of MoH RU in neurosurgery department during 2014-2019 year.
All patients were undergone the spectrum of analyses, including endocrine status assessment, clinical, biochemical, hormonal (GH, LH, FSH, prolactin, TSH, testosterone and others), radiological (CT/MRI of Turkish saddle), and histological study. All patients have pituitary adenoma more than 5 cm.
Depending on the type of cells found on the histological study, patients with NFPA (chromophobic adenomas) were divided into 3 groups: 1st group – small cell (undifferentiated) chromophobic adenoma – 8 patients, 2nd group – large cell chromophobic adenoma – 7 patients, and 3rd group – oncocytoma -6 patients.
Results: Preliminary analysis of the research showed that among the observed patients the most disposed to invasive total growth had patients of the 1st group with small cell histological structure of NFPA. Besides, this patients had more frequent tumor relapse in post-operative period – 3 patients (37.5%), had acute manifestation of the disease with general cerebral symptoms and neuroendocrine disturbances (secondary amenorrhea in female, potency and libido decrease in male, metabolic syndrome, visual disturbances and others). Two female patients aged 27.5 from the 1st group were undergone repeated selective pituitary adenomaectomy 3 times.
Conclusion: 1. Small cell NFPA have the most aggressive growth and tumor relapse. 2. Following research is necessary to study the markers of aggressiveness in all 3 groups.

EP-05 - THE MRI CHARACTERISTIC OF THE CHIASMAL-SELLAR REGION OF THE PITUITARY GLAND IN PATIENTS WITH VARIOUS TUMORS

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Aim of Investigation: To study the tomographic characteristic of the chiasmal-sellar region (CSD) in patients with volumetric formations of the hypothalamic-pituitary region.
Material and Research Methods: We evaluated the period from 2018 to 2020. Forty four patients with various pituitary adenomas were examined. Of these, men - 25 (56.8%), women - 19 (43.2%). Average age: men amounted to 37.12 years, women - 38.15 years. The research methods included: 1) general clinical (study of endocrine, neurological status, anthropometry 2) instrumental (perimetry for all colors, fundus, visual acuity, ECG, densitometry, CT / MRI of the Turkish saddle, etc.), 3) hormonal blood tests (STH, IGF-1, LH, FSH, PRL, TSH, ACTH, prolactin, etc.)
Research Results: Among the 44 patients examined, various formations of the Sellar region were identified: non-functional pituitary adenoma (NFPA) - 21 patients, prolactinoma - 10, Cushing's disease - 7, craniopharyngoma -2, acromegaly -4.
Depending on the size of the pituitary adenoma, the following pituitary changes were found on CT / MRI: microadenomas (<10 mm) - 2 patients (4.5%), mesoadenomas (11-20 mm) - 3 patients (6.8%), macroadenomas (up to 30 mm) - 14 patients (31.8%), giant - (more than 30 mm) - 25 patients (56.8%)
Distribution of patients according to topographic anatomical classification of the growth side of the pituitary adenoma B. Kadashev (2007) showed that the most frequently observed pituitary adenomas with endosuprasellar growth - 13 p-s(29.5%), with infracellular growth - 2 (4.5%), with laterosellar growth - 3 (6.8%) , with an antesellar growth of -1 (2.3%), with a retrocellular growth - 1 (2.3%), with a total growth option - 24 p-s (54.5%).
Conclusion: 1) Among the examined 44 patients with volumetric formations of the sellar region, patients with giant pituitary adenomas (more than 3 cm) predominated - 25 cases (56.8%). 2) The most common endo-suprasellar growth of the neoplasm was 13 cases (29.5%).

EP-06 - "THE COMPARISON BETWEEN NEUROLOGICAL SYMPTOMS AND HISTOLOGICAL STRUCTURE IN CHIASM AND SELLAR REGION GIANT TUMORS"

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Aim of the Research: To study special features of pituitary adenoma (PA) clinical manifestation depending on hormonal characteristic and histological structure, and reveal correlation between clinical manifestation and tumor pathology.
Material and Methods: Outcomes of surgery in 66 patients with PA were analyzed. Age of patients at surgery was from 18 to 71 years. Mean age of patients – 44 years.
According to K. Thapar classification (1977), 4 patients (6%) had a corticotropinoma, 11 patients (17%) had somatotropinoma, 11 patients (17%) had prolactinoma and remaining 40 patients (60%) had non-functioning pituitary adenomas (NFPA). PA was diagnosed in according with clinical signs, hormonal tests, neuroendocrine status and histological analysis. All patients were undergone surgical treatment by transsphenoidal access Center of Endocrinology of MoH RU in neurosurgery department during 2018-2020 years.
Results: According to histology, 47 adenomas (71%) were chromophobe, 15 adenomas (23%) were acidophilic and 2 adenomas (3%) were basophilic, and 2 adenomas (3%) were defined as compound.
Comparison between histological structure and clinical manifestation revealed that chromophobe prolactinomas showed progressive course, big size of the tumor with the tendency to extrasellar growth and barely respond to conservative treatment.
Acidophilic prolactinomas performed gradual onset with the endocrine dysfunction, body mass changes, dysmenorrhea, galactorrhea, intracranial hypertension and erectile dysfunction in men.
Histology in 4 patients revealed basophilic structure of PA and clinical manifestation have seen in short period.
Clinical manifestation of NFPA presented in all patients with the focal symptoms, including dislocation and hypertension syndromes, visual and oculomotor disturbances. Besides, there apoplexy symptoms have seen which degree depended on the course of disorder.
Conclusion: In according with literature reviews and own study results early clinical symptoms of PA should be evaluated opportunely and indications for surgery should be defined taking into account clinical forms which decreases the complications development risk.

EP-07 - "THE CLINICAL FEATURES OF PATIENTS WITH TYPE 1 AND TYPE 2 DIABETES MELLITUS UNDER HEMODIALYSIS"

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Aim of Investigation: To study clinical characteristics of patients with type 1 and type 2 diabetes who received hemodialysis in 2017 year.
Material and Research Methods: We for the period from January, 01.2017 to December, 31, 2017 year 102 patients with type 1 and type 2 diabetes mellitus were examined. Of these, men - 45 (44.1%), women - 57 (55.9%). Average age: men amounted to 57.12 years, women - 58,15 years. 20 of them were urgently received hemodialysis.
The research methods included: 1) general clinical (study of endocrine, neurological status, anthropometry 2) instrumental (fundus, visual acuity, ECG, densitometry, Ultrasound of internal organs and dopplerography of the main arteries of the head, etc.), 3) biochemical tests (Hb1AC, glycemic profile, urea, creatinine, lipid spectrum, coagulogram), 4) hormonal blood tests (insulin, C-peptide etc.).
Research Results: Depending on the degree of diabetic encepha-

lopathy, all observed patients were divided into 3 groups: 1 gr - 23 patients with diabetic nephropathy of 4-5 stages with CBI 1 st (chronic brain ischemia); 2 gr. - 45 patients with diabetic nephropathy of 4-5 stages with CBI 2 st; 3 gr. - 34 patients with diabetic nephropathy of stages 4-5 with CBI 3 st.
Analysis of clinical and medical history studies showed that the duration of the disease prevailed in patients of the 3rd group - 22.5 years, while in patients of the 2nd group - 15.6 years, and in patients of the 1st group - 11.7 years.
22 patients were died during year. Stage 5 diabetic nephropathy was detected in all patients.
Conclusion: 1) Among the examined 102 patients, patients with a 2 degree of chronic cerebral ischemia prevailed; 2) The duration of the disease prevailed in patients of the 3rd group - 22.5 years.

EP-08 - THE NEUROLOGICAL FEATURES OF PATIENTS WITH DIABETIC NEPHROPATHY V ST.

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Aim of Investigation: To study neurological characteristics of patients with type 1 and type 2 diabetes who received hemodialysis.
Material and Research Methods: We for the period from January, 01.2017 to December, 31, 2017 year 102 patients with type 1 and type 2 diabetes mellitus were examined. Of these, men - 45 (44.1%), women - 57 (55.9%). Average age: men amounted to 57.12 years, women - 58,15 years. 20 of them were urgently received hemodialysis.
The research methods included: 1) general clinical (study of endocrine, neurological status, anthropometry 2) instrumental (fundus, visual acuity, ECG, densitometry, Ultrasound of internal organs and dopplerography of the main arteries of the head, etc.), 3) biochemical tests (Hb1AC, glycemic profile, urea, creatinine, lipid spectrum, coagulogram), 4) hormonal blood tests (insulin, C-peptide etc.).
Research Results: Depending on the degree of diabetic encephalopathy, all observed patients were divided into 3 groups: 1 gr - 23 patients with diabetic nephropathy of 4-5 stages with CBI 1 st (chronic brain ischemia); 2 gr. - 45 patients with diabetic nephropathy of 4-5 stages with CBI 2 st; 3 gr. - 34 patients with diabetic nephropathy of stages 4-5 with CBI 3 st.
Analysis of neurological status showed various disorders. Patients of the 1st group had headaches, noise in the head, memory loss, and in the neurostatus the disappearance of surface reflexes, anisoreflexia. Patients of the 2nd group experienced headaches, noise in the head, memory loss, depression, sleep disturbances, attacks of transient ischemic attacks, and the appearance of pathological Babinsky symptoms from 2 sides was characteristic in the neurostatus. In the 3 group of patients, we observed a history of stroke in 5 cases (14.7%), in neurostatus hemiparesis in 5 patients (14.7%), dysarthria - 4 cases (11.7%), pseudo-bulbar syndrome - 6 patients (17.6%), increased muscle tone in spastic and plastic type - 11 patients (32.3%).
Conclusion: 1) Among the examined 102 patients, patients with a 2 degree of chronic cerebral ischemia prevailed; 2) Severe neurostatus disorders were detected in patients of group 3.

EP-09 - MULTIPLE ENDOCRINE NEOPLASIA: A CASE SERIES OF 7 FAMILIES

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Background: Multiple endocrine neoplasia (MEN) is a rare genetic syndrome characterized by occurrence of tumors involving two or more endocrine glands. Four types are described: MEN1, MEN2, MEN3 and the recently identified MEN4. Due to the complexity of the syndromes, it is difficult to manage these patients.
Aim: Describe the clinical features of 7 individuals with a diagnosis of MEN1 or MEN2 and identify current challenges in clinical practice.
Case Series:
1. Female, 48, presented with appendicitis at the age of 40. Pathology reported a neuroendocrine tumor (NET). Later, she was diagnosed with primary hyperparathyroidism (PH) and pituitary adenoma. The diagnosis of MEN1 was made at 44. Both her children are carriers.
2. Female, 38, presented with prolactinoma at 18 years, for which she took dopamine agonists. Due to infertility, she was referred to assisted reproductive technology, where she was diagnosed with PH and NET. The diagnosis of MEN1 was made at 37.
3. Female, 66, presented with acute pancreatitis at 49 years. An abdominal MRI revealed *nodular* lesions of the pancreas. The pathology reported NET. Later, she was diagnosed with PH and pituitary adenoma. The diagnosis of MEN1 was made at 59. She has two children, 1 carrier.
4. Female, 50, presented with hypothyroidism. A thyroid ultrasound revealed a large nodule. The cytology reported medullary thyroid carcinoma (MTC). The diagnosis of MEN2 was made at 46. She has five children, 2 carriers. Both underwent prophylactic surgery.
5. Female, 74, presented with goiter for which she had total thyroidectomy (TT). The cytology reported MTC. The diagnosis of MEN2 was made at 68. She has 3 children and 4 grandchildren, all carriers. One of them, 18 years, rejected prophylactic surgery. All other family members underwent TT.
6. Male, 60, presented with MTC and pheocromocytoma at 40 years. Genetic testing revealed no RET mutation. He has 3 children.
7. Male, 58, diagnosed with acromegaly at 36 years, for which he had surgery and takes somatostatin analogs. At 46, he underwent left nephrectomy for a nodular lesion in the kidney. At 48, he presented PH. Genetic testing revealed no MEN1 mutation. Suspicion of MEN4.

Discussion: From our series, the main clinical challenges were:
Pregnancy in MEN1 patients (case 2);
Rejection of a prophylactic surgery (case 5);
Clinical diagnosis and surveillance after a negative genetic screening (cases 6 and 7).
We reviewed the literature and discuss the management of these patients.

EP-10 - LONG TERM FOLLOW-UP OF A RARE PITUITARY TUMOR: A MIXED GANGLIOCYTOMA-ADENOMA

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Aim: To report a case of a rare mixed gangliocytoma-adenoma secreting prolactin with over 25 years of follow-up, emphasizing its distinctive response to therapy.
Background & Methods: Mixed pituitary gangliocytoma-adenomas are exceedingly rare, accounting for 0.25%-1.26% of all sellar tumors,1 and may secrete growth hormone, or, less frequently, prolactin or cortisol.[1,2]
This work involved a review of the patient's clinical file and a brief literature search.
Results: A 15-year-old female patient presented with a perception of visual field's reduction. Temporal hemianopsia was documented and a brain magnetic resonance (MRI) was performed revealing a 3 cm wide pituitary lesion compatible with macroadenoma. On completing the anamnesis she also reported headaches, nausea, vomiting that had been evolving for 3 years, and primary amenorrhea.
Due to elevated prolactin levels (4000-6000 ng/mL), a diagnosis of macroprolactinoma was assumed and bromocriptine was initiated with an incomplete biochemical response and slight tumor shrinkage. The treatment was switched to cabergoline with discretely better outcomes.
At age 23, when the patient initiated follow-up at our hospital, she presented prolactin of 1202 ng/mL (under cabergoline) and gonadal insufficiency. The MRI showed a 5 cm sellar and suprasellar mass, compressing the optic chiasma, the III ventricle, the anterior cerebral and right middle cerebral arteries. Given the tumor's extension and refractoriness to medical therapy, surgical resection was attempted with partial excision of the mass. The pathology revealed a prolactin-producing pituitary adenoma with extensive ganglionic metaplasia.
After the intervention, the patient reported some clinical improvement. Biochemically, however, there was persistence of hyperprolactinemia and the MRI (3 months post-surgery) showed a 4.8x4.05 cm lesion.
Due to the location of the mass, a reintervention has not been performed and the patient has been kept under surveillance and treatment with cabergoline. Despite incomplete biochemical response and the patient remaining in amenorrhea, there has been no further deterioration of the optic fields or reaggravation of the remaining symptoms.
Conclusion: The presence of prolactin >500 ng/mL and a pituitary mass was very suggestive of a macroprolactinoma however, the histology revealed concomitant presence of ganglionic cells. These tumors, currently classified as mixed gangliocytomas-adenomas,[1] may have a good biochemical response to dopamine agonists, but there is usually no significant tumor shrinkage.[3] They are also less sensitive to radiotherapy[2–4] and complete resection is ideal.[2] In this case, however, a reintervention was deemed of unfavorable risk-benefit and the patient has been kept under careful surveillance.

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EP-11 - ASYMPTOMATIC MICROADENOMA PITUITARY APOPLEXY INDUCED BY CORTICOTROPHIN-RELEASING HORMONE IN A 14-YEARS-OLD GIRL WITH CUSHING'S DISEASE

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Background: In pediatrics the occurrence of a pituitary infarction or apoplexy is a rare event and only a few numbers of cases associated with pituitary adenomas have been described. Similarly, when a pituitary haemorrhagic or ischemic infarction occurs the chance of this result in a spontaneous cure of the underlying adenoma, is even smaller. We report an unusual case of Cushing's disease (CD) remission by asymptomatic microadenoma pituitary apoplexy induced by corticotrophin-releasing hormone in a 14-years-old girl.
Case Report: A 14-year-old white girl referred to our appointment for evaluation of possible Cushing's syndrome (CS). She presented with a 6 months history of centripetal obesity, moon facies, a buffalo hump, purple thighs striae, acne, hirsutism, amenorrhoea, arterial hypertension and exuberant acne. Laboratorial results revealed an urinary free cortisol (UFC) excretion of 195.3 nmol/mmol Cr (normal, 0.5–20.0 nmol/mmol Cr), a 24h UFC of 529.2 µg/24h (normal, 4.3-176 µg/24h), ACTH levels of 28.6 pg/mL and a high-dose dexamethasone suppression test cortisol suppressed in 67%. During CRH stimulation (100 µg IV bolus) her plasma cortisol increased by 28% over baseline and her plasma ACTH increased by 86% over baseline, indicating pituitary disease. Magnetic resonance imaging (MRI) of the pituitary gland showed a pituitary microadenoma (6x5 mm). Two months after the CRH stimulation test a bilateral inferior petrosal sinus sampling (BIPSS) + CRH stimulation was performed. BIPSS presented an absence of response to CRH stimulation maintaining overlapping levels of ACTH. The patient was evaluated in an appointment and presented a clinical improvement of CS stigmas, analytical resolution of hypercortisolism and an imagiological reduction of tumor size (4x3 mm) with MRI results showing a hemorrhagic component favoring the diagnosis of pituitary apoplexy after CRH stimulation test. The patient denied any severe episodes of headache, nausea, vomiting or visual changes.
Discussion: This is a very rare case of DC remission after asymptomatic pituitary apoplexy microadenoma in pediatric age occurring after CRH stimulation test. Since CRH stimulation test is an evaluation tool frequently used in ACTH-depend CS assessment, clinicians should be aware about the possibility of pituitary apo-

plexy. An unusually severe headache within a few days of a CRH stimulation test, or like in this case, an improvement in Cushing's syndrome clinical condition despite any sign of pituitary apoplexy should raise the suspicion of this diagnosis.

EP-12 - PREDICTIVE FACTORS FOR ACROMEGALY REMISSION IN PATIENTS UNDERGOING TRANSSPHENOIDAL SURGERY

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Aim: To evaluate predictive factors of disease remission in acromegaly patients followed at our hospital centre.
Background & Methods: Acromegaly is a chronic and rare multisystem disease characterized by somatic overgrowth, multiple comorbidities and premature mortality. Transsphenoidal (TSS) surgery is the first line therapy recommended in most patients. Reportedly, only 50% to 70% of cases attain remission after an initial surgery.
A retrospective study, based on clinical records of patients with acromegaly who undergone TSS surgery from February/1988 and August/2019 was performed. Remission criteria was defined as a nadir growth hormone (n-GH) in the oral glucose tolerance test (OGTT) <1µg/L until 3 months after surgery. Analysis of clinical, biochemical, imaging and anatomopathological variables and their predictive role in remission of acromegaly. Biochemical variables studied were: pre and post-operative n-GH in the OGTT, post-operative GH levels, and ratio of upper limit of normal (rULN) range IGF1 in the pre and postoperative period. The *p*-value<0.05 was considered statistically significant.
Results: Fifty-eight patients were included. The average age at diagnosis was 46.97±13.46 years, with 62.10% being female. Surgical remission was achieved in 18 patients (31.0%).
Older ages was seen in the remission group (56.94±14.80 years *vs* 42.48±10.12 years; $p<0.001$), with no difference in sex ($p=0.920$) and preoperative body mass index ($p=0,770$).
Lateral invasion of the cavernous sinus, optic chiasm compression and suprassellar extension were associated with recurrence ($p=0.001$, $p=0,012$, $p=0,014$, respectively).
Regarding the size of the tumour, there was a tendency towards larger tumors in the group without remission [18mm (IQR:15.9) *vs* 14 mm (IQR:10.70)], despite not being statistically significant ($p=0.083$).
There were no significant differences in the remission vs non-remission group for granulation pattern ($p=0.280$) and Ki-67% ($p=0.999$), with complete resection associated to remission ($p=0.025$).
The preoperative n-GH, postoperative random GH value, and postoperative rULN range IGF1, were the most important predictors of remission, with the latter having the largest area under the curve (AUC=0.744, $p=0.014$; AUC=0.843, $p<0,001$; AUC=0.975, $p<0.001$, respectively).
The postoperative rULN range IGF1 from 1.35 one week after surgery predicted remission with 94% of sensitivity and 94% of specificity.
Conclusion: In this study, the postoperative rULN range IGF1 was the most important predictor of remission. Older age that was seen in the remission group, can be explained by this group of patients having smaller tumors.

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EP-13 - INCIDENTAL VERSUS SYMPTOMATIC CLINICALLY NONFUNCTIONING PITUITARY ADENOMAS: PRESENTING FEATURES AND CLINICAL MANAGEMENT. ARE THEY DIFFERENT?

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Backgroud: Clinically nonfunctioning pituitary adenomas (CNFPAs) are among the most common tumors in the sellar region. They frequently remain undetected until mass effect symptoms develop or less frequently apoplexy occurs. However, currently, head imaging is performed commonly for many other indications, which may increase discovery of incidental CNFPAs. Since current presentation and outcome data are based mainly on older series, a characterization of a contemporary CNFPA cohort was necessary.
Aim: To determine the prevalence of incidental presentation and hypopituitarism in a cohort of patients observed with CNPA over a decade, including patients with micro to macroadenomas, under clinical observational or surgical therapy.
Methods: We retrospectively analyzed patients aged ≥ 18 years who presented at our center between 2010 to 2020 with an apparent CNFPA, defined as a pituitary adenoma on imaging studies in a patient without clinical or biochemical evidence of a hormone-secreting tumor. The patient's clinical history, laboratory data and pituitary image were collected and they were categorized into incidental or symptom groups that were compared. Inclusion criteria included normal prolactin level for lesions <9 mm or a prolactin level < 100 ng/mL for lesions ≥ 10 mm in maximal tumor diameter.
Results: We included 119 patients, of which 52.9% were males, with a mean age of 55.8±19.0 years. Presentation was incidental in 47.1% of patients and due to tumor symptoms in 52.9%. Many patients had unappreciated signs and symptoms of pituitary disease, sometimes with severe visual defects (visual defects were present in 28.6% and 47.6% of patients in incidental and symptomatic groups, respectively). In the symptomatic and incidental groups, 75% and 41.1%% of patients had hypopituitarism, respectively. Most tumors were macroadenomas (86.7%). Only 21.2% of patients which presented incidentally had microadenoma. 28.6% of patients with microadenomas higher than 6mm had hypopituitarism.

A percentage of 48.2% of the patients who presented incidentally were submitted to surgery (4.2% - underwent reintervention and 15% underwent radiotherapy comparatively to 74.6% of those who presented with symptomatology (19.1% - underwent reintervention and 17% underwent radiotherapy).
Conclusion: Nowadays, patients with CNFPAs most commonly presents incidentally, with previously unrecognized hypopituitarism and symptoms that could have led to early diagnosis if there was a greater degree of clinical suspicion. Our data support screening all micro and macro-CNFPAs for hypopituitarism. Many patients with CNFPAs still show signs of a mass effect on presentation, sometimes severe visual defects, suggesting the need for more awareness of pituitary disease.

EP-14 - PROLACTINOMAS IN PREGNANCY: POST-PARTUM DOPAMINE AGONIST REQUIREMENT

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Aim: Assess dopamine agonist therapy requirements after pregnancy in patients with prolactinomas followed at a tertiary centre.
Background & Methods: Prolactinomas are the most frequent pituitary tumors, being diagnosed before 40 years old ten times more often in women. These tumors often lead to hypogonadism and subfertility. Treatment approach with dopamine agonists (DA) allows fertility to be restored and pregnancy to be achieved in the majority of cases.
Pregnancy lactotrophs stimulation may lead to tumor enlargement, nevertheless, post-partum remission is described in 12%-41% of cases. Older age, lower prolactin levels and smaller adenomas at diagnosis have recently been identified as remission predictors.
A retrospective study was performed by analysis of medical records of a tertiary centre. From 72 women diagnosed with prolactinomas,10 patients who achieved pregnancy during follow-up were included.
Age and symptoms at diagnosis, time of follow-up, prolactin measurements, tumor radiographic features, treatment approaches, drugs and doses were collected before and after pregnancy.
Results: Mean age at diagnosis was 26.1 ± 6.2 years old and mean time of follow-up was 4.9 ±5.4 years. Median baseline prolactin level was 274 ±183.4 ng/ml.
The presenting symptoms were amenorrhea in seven cases (70%), galactorrhea in five (50%), and oligomenorrhea in 1 patient.
Before conception half of patients had microprolactinomas while the remnant had macroprolactinomas. Tumor extrasellar extension was present in 3 tumors with ≥1cm.
DA were used before pregnancy in all women. Bromocriptine was the preferred treatment at diagnosis in 8 patients, with cabergoline being used in two cases. The drug was maintained before conception in 9 of these.
There was one case of DA withdrawal previously to conception. Medication was discontinued in the first trimester of pregnancy in six patients, and two maintained afterwards.
Prolactin normal levels were reached after delivery in 6 cases. Two patients achieved remission without DA including the microprolactinoma patient who had stopped medication in preconception. No significant predictors of remission were identified.
At last appointment 4 patients required DA, half were treated with bromocriptine 2.5 mg daily, both microprolactinomas, and half with cabergoline 1 mg per week, one micro and one macroprolactinoma.
Conclusion: DA treatment in prolactinomas has well established successful results. After pregnancy tumor enlargement and remission have both been described. In this ten cases study tumor remission was achieved in two patients after pregnancy and disease controlled with DA in 4 patients. No tumor enlargement or predictors of remission of disease after pregnancy were identified.

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EP-15 - PROLACTINOMAS: THE PATIENTS, THE TUMOR, THE EFFECT IN PITUITARY SECRETION

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Aim: Assess patient demographics, tumor characteristics and effect in pituitary secretion of prolactinomas in a tertiary centre.
Background & Methods: Prolactinomas are frequent pituitary adenomas in clinical practice. These prolactin secreting tumors may affect a wide variety of patients and have diverse presenting features including compromised secretion of other pituitary hormones.
A retrospective longitudinal study was performed by analysis of medical records. Patients followed at the tertiary centre due to prolactinoma diagnosis with last appointment between 2016 and 2020 were included totalizing 110 patients. Pituitary hormones, patient demographics, presenting symptoms, tumor radiographic features, and therapeutic approach were assessed at intervals between diagnosis, six months, one, two and five years.
Compromise of pituitary hormones secretion was evaluated based on documented diagnosis of secondary adrenal insufficiency, secondary hypothyroidism or hypogonadism.
Results: The mean age at diagnosis was 36.9±14.8 years old. Women were 66.6%. Median baseline prolactin was 662 ng/mL (range of 19 660), decreasing to 24.4 ng/mL and 19.6 ng/mL at one and two years respectively.
Amenorrhea (56.2%) and galactorrrhea (43.8%) in women, headaches (27%), loss of libido (21.6%) and impaired vison (18.9%) in men were the most frequent presenting symptoms.
Microprolactinomas were 31.5% (n=34), macroprolactinomas 63.9%(n=69), and 3 were giant prolactinomas. The latter were diagnosed only in men, while 91.2% and 55.1% of micro and macroprolactinomas were diagnosed in women, respectively.
Suprasellar was the most frequent tumor extension 42.2%(n=37), while 28.3% (n=26) had multisided invasion.
Treatment approaches included active surveillance (n=4) and single therapy with dopamine agonists (DA) in 87.3% (n=96). Nine DA refractory cases required combination between surgery, radiotherapy, and, in one case, temozolamide.
At last appointment microprolactinoma had controlled disease in

54.5% (n=18), macroprolactinomas in 62.3% (n=43) and 33% of giant prolactinomas (n=1).
Secondary adrenal insufficiency was present in 17.2% (n=19) and secondary hypothyroidism in 27.3% (n= 30). Diabetes insipidus was diagnosed in one case.
During follow-up a lower number of hormone measurements was identified in all hormone series in comparison to diagnosis, except prolactin.
Conclusion: Prolactinomas represent a heterogeneous pituitary tumor type with evolution assessed through prolactin levels and radiological characteristics. Despite usual DA therapy response, prolactinoma effect in other pituitary hormones may potentiate disease burden through secondary adrenal insufficiency and secondary hypothyroidism. Further studies are required to document a possible hormone secretion restoration in responsive tumors.

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EP-16 - BIOCHEMICAL CONTROL RESPONSE RATES WITH FIRST GENERATION SOMATOSTATIN ANALOGUES IN THE REAL-LIFE SETTING: THE EXPERIENCE OF A TERTIARY CENTER

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Background and Aim: Acromegaly is a rare endocrine disease characterised by increased production of growth hormone (GH) and insulin-like growth factor (IGF-1) due to a pituitary tumour. The mainstay of treatment is transsphenoidal surgery, but long-term pharmacological treatment is often required, usually consisting of long acting somatostatin analogues (SSA).The main goal of treatment is an age-normalized serum IGF-1 value. Our study aims to evaluate the proportion of patients achieving biochemical control and to determine time to biochemical control among a cohort of patients with acromegaly treated at a tertiary pituitary center.
Methods: Patients diagnosed with acromegaly treated with SSA monotherapy as adjuvant (following surgery and/or radiotherapy) or primary medical therapy from January 2011 to August 2019 were included. Socio-demographic, clinical and biochemical data were reviewed retrospectively; IGF-1 index was calculated by dividing IGF-1 levels by the age and gender-adjusted upper limit of normal (ULN). Biochemical control was defined as serum IGF1≤1.3ULN; additionally, we created a composite outcome measure of IGF1≤1.3ULN and random GH<1.0 ug/dL. Both were used to assess biochemical response at 6 months and at the last available evaluation.
Results: We included 37 patients (62.2% females) with a mean age at diagnosis of 47.0±12.8 years and a median follow-up time of 9.0(IQR 5.6-16.7) years. Treatment with SSA (octreotide or lanreotide) followed surgery in 29 patients (10 with radiotherapy treatment): the remainder were treated solely with SSA.
At treatment initiation, the median serum IGF-1 and IGF-1 index were 590.5 (442.5-717.0) ng/mL and 2.1 (1.6-2.7), respectively. Median serum IGF-1 levels and IGF-1 index showed a statistically significantly decrease, respectively to 261.0 (223.0-437.0) ng/mL and 1.1(0.8-1.5) at 6 months (p<0.001). At 6 months, the proportion of patients achieving biochemical control and the composite measure outcomes was 64.9% (n=24) and 32.4% (n=12), respectively.
Overall, median time to first IGF-1≤1.3ULN was 0.5(0.5-1.0) years. Median duration of treatment was 4.5(2.7-11.0) years. At the last follow-up, median serum IGF1 and IGF index were 196.0 (154-263.5) ng/mL and 0.9 (0.6-1.2) and the proportion of patients that attained biochemical control was 83.8% (n=31); serum IGF-1 pre-treatment and at 6 months were statistically significantly lower in this subset of patients (U=35.5, p<0.001 and U=15, p=0.001) but no difference was found for gender, age at diagnosis and duration or modality of SSA treatment (adjuvant versus primary).The composite measure was achieved by 29.7% but interpretation is undermined by missing data on random serum GH values.
Conclusion: In our study SSA treatment was a valuable tool to attain long-term biochemical control with an approximately 84% response rate in this cohort including both naïve and previously treated acromegaly patients. However, the retrospective nature of the study may result in higher response rates.

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EP-17 - CLINICAL CHARACTERISTICS AND BIOCHEMICAL CONTROL WITH MULTIMODALITY THERAPY OF AN ACROMEGALY COHORT: EXPERIENCE OF A TERTIARY CENTER

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Background and Aim: Acromegaly is a rare endocrine disease

characterised by increased production of growth hormone (GH) and insulin-like growth factor (IGF1) due to a pituitary tumour. Our study aims to assess clinical and radiographic characteristics at diagnosis and to determine prevalence of biochemical control with long-term multimodality therapy in a pituitary outpatient clinic.

Methods: Patients diagnosed with acromegaly at our center between January of 1976 and June 2020, with available data at diagnosis, were reviewed and analysed for baseline characterisation of the cohort. A minimum of one year of follow-up after diagnosis was established as exclusion criteria for long term follow-up analysis. IGF-1 index was calculated by dividing IGF-1 levels by the age and gender-adjusted upper limit of normal (ULN). Surgical remission defined by IGF1 and random and post-OGTT GH values established by the 2014 Endocrine Society Guidelines. Biochemical control at follow-up was defined as serum IGF1≤1.3ULN.

Results: For baseline characterisation at diagnosis, 89 patients (57.3% females), were included with a mean age at diagnosis of 48.1±13.0 years. Median serum IGF-1 and IGF-1 index were 659.0 (IQR 491.0-841.0) ng/mL and 2.3 (1.8-3.1), respectively. Macroadenomas were present in 80.1% (n=72) with a median maximum tumour diameter of 18.0 (10.5-29.5) mm. Men had a statistically significantly lower age at diagnosis when compared to females (43.1±13.6 years vs 51.7±11.4 years; p=0.002); tumour size and IGF1 levels at diagnosis did not differ by gender.

Within the subset of patients with sufficient follow-up data (n=76), the first line treatment modality was surgery in 81.6% (n=62), followed by primary and preoperative medical therapy in 15.8% (n=12) and 2.3% (n=1), respectively; one patient refused treatment. Surgical remission occurred in 50.8% (n=32) of the patients; logistic regression was performed adjusting for age at diagnosis, gender, serum IGF1 and tumour size at diagnosis. Smaller tumour size was associated with an increased likelihood of long term sustained IGF1 normalization after surgery (p<0.001). The remaining patients (n=31) received medical therapy, 38.7% (n=12) were submitted to at least one more surgery and 32.3% (n=10) to radiation therapy.

Overall, median follow-up time from diagnosis was 8.7 (3.5-13.8) years; at the last follow-up 86.8% (n=66) of the patients had achieved biochemical control. Among the patients with abnormal IGF1 levels (n=10), median serum IGF-1 and IGF-1 index were 377.0 (309.5-567.5) ng/mL and 1.7 (1.5-2.6), respectively. Primary reasons for suboptimal control included non-compliance/refusal of treatment (n= 4) and resistance to medical therapy (n=3); additionally 3 patients were still undergoing adjustment of therapy.

Conclusion: With a multidisciplinary approach and long-term follow-up in an experienced pituitary center, most patients will ultimately achieve sustained biochemical control.

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EP-18 - AN UNUSUAL CAUSE FOR 68-GA-DOTATOC UPTAKE IN A PANCREATIC GRAFT

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Backgroud: Acessory spleen (AS) is an anomaly of splenic embryology present in about 10% of normal population, mostly located in the splenic hilum. Intrapancreatic acessory spleen (IPAS) accounts for 16% of all AS.[1,2] It is usually incidentally identified on imaging studies like computed tomography (CT) scan, magnetic ressonance imaging (MRI) or nuclear medicine imaging.[1] CT or MRI shows a pancreatic mass with attenuation or signal intensity similar to pancreatic neuroendocrine tumours (P-NETs). 68-Ga-DOTANOC is the gold standard in NETs diagnosis but caution should be taken with possible false positive results.[2,3] We present a case of IPAS occurring in a transplanted pancreas.

Case Report: A 29 years-old female with type 1 diabetes underwent renopancreatic transplant in November 2019. Surgery was uneventful and pancreatic graft showed good function. On the 4th day after transplant, a contrast-enhanced CT incidentally showed a 20 mm hypervascular nodule in the pancreatic graft's tail. MRI described the same lesion, hyperintense on T2-weighted and hypointense on T1-weighted sequence, in the upper part of the tail of pancreatic graft, suggesting a potential neuroendocrine tumor (NET). 18-Fluorodeoxyglucose positron emission tomography ([18-F] FDG-PET) did not show FDG uptake and CEA and CA 19-9 levels were in the normal range. The diagnostic approach continued with a 68Ga – DOTANOC and PET-CT, more sensitive and specific for neuroendocrine tumors (NET), showing a focal area of uptake in the pancreatic graft's tail (SUVmax=12.9). Blood tests showed a high chromogranin A level of 576 ng/mL (reference value <100 ng/mL); however, the patient was under proton pump inhibitors treatment. A second measurement of chromogranin A five months later, without the referred medication, was also high (215 ng/mL). The diagnosis of an IPAS was suspected, but in the scenario of a transplanted pancreas with a nodule not amenable to transcutaneous biopsy and the risk of being a tumor in an imunossuppressed patient, it was decided to proceed to enucleation of the nodule. Histologic examination of the pancreatic graft's nodule revealed an intrapancreatic accessory spleen.

Conclusion: To our knowledge this is the second reported case of an IPAS in a transplanted pancreas. Albeit its rarity, it must be considered in the differential diagnosis of a pancreatic mass, particularly when a pancreatic NET is initially suspected. A combination of imaging tools and eventually the use of proper diagnostic immunocytologic features would be necessary for the correct diagnosis of IPAS, in order to avoid unnecessary surgery.

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EP-19 - DOES VOLUMETRIC MRI (3D-SGE SEQUENCE) IMAGING ENHANCE DIAGNOSTIC RATES AND IMPROVE TREATMENT IN CUSHING'S DISEASE?

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Cushing's disease (CD) is an endocrine disorder, in which treatment and diagnosis have always been challenging. The pituitary tumours in CD are mostly microadenomas and 50% of them has a size less than 5 mm, therefore it is not easy to detect them by conventional MRI. Volumetric MRI (3D-SGE, spoiled-gradient echo 3D sequence) performs high spatial resolution scans by using very thin slices (1 mm) and it gives us the possibility to find small lesions in the pituitary gland. The aim of this work is to present an overview of pituitary volumetric MRI in the diagnosis of Cushing's disease and report the clinical utility and diagnostic accuracy of this imaging.
We retrospectively searched about 20 patients with Cushing's disease who were treated at St Bart's Hospital in London from 2015 to 2018. All patients were evaluated by standard biochemical tests for Cushing's syndrome. These patients underwent for the localization of pituitary tumour by both SE (spin-echo) and 3D-SGE (spoiled gradient echo) techniques after the confirmation of ACTH-dependent cortisol secretion. Patients with pituitary macroadenomas (4 patients), who had positive results in both sequence (4 patients) and who was not in remission were excluded during the research. We compared the results of both sequences. As a result, 3D-SGE scans were positive in 3 patients. The interesting point was that all these patients were negative in conventional MRI (SE sequence) and were only defined by volumetric MRI. The size of these microadenomas varied between 3-6 mm. Then these three patients underwent for transsphenoidal surgery. The result of histopathology confirmed the diagnosis of Cushing's disease and all patients were in remission. 3D-SGE MRI sequence is the best option when the conventional MRI is negative and should be used in the diagnosis and management of Cushing's disease.

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EP-20 - A GASTROINTESTINAL STROMAL TUMOUR MIMICKING A PHEOCHROMOCYTOMA IN A PATIENT WITH NEUROFIBROMATOSIS TYPE 1

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Introduction: Neurofibromatosis type 1 (NF1) is a common neurocutaneous condition with autosomal dominant inheritance.[1] These patients can develop several endocrinopathies with significant morbidity.[2] We describe a patient with suspected recurrence of pheochromocytoma which revealed to be a gastrointestinal stromal tumor (GIST).
Clinical Case: A 52-year-old male with history of NF1 and bilateral adrenalectomy (complete resection) 11 years before due to a bilateral pheochromocytoma was referred to our centre with suspected malignant pheochromocytoma. He had also been diagnosed with primary hyperparathyroidism, due to clear cell parathyroid adenoma of the right upper parathyroid gland, treated by selective parathyroidectomy and right hemithyroidectomy due to papillary thyroid microcarcinoma. He reported sporadic headaches, but denied paroxysms or high blood pressure. Blood tests showed plasma metanephrines <6 pg/mL [normal range (NR) <65] and normetanephrines 165 pg/mL (NR <196). The 24-hour urinary metanephrines revealed: total metanephrines 1413 µg/24h (NR 329-1263), metanephrines 164 µg/24h (NR 64-302), normetanephrines 1007 µg/24h (NR 162-527), and 3-methoxytyramine 242 µg/24h (NR 103-434). The abdominal computed tomography (CT) scan showed a right retroperitoneal nodule with 13mm, posterior to the inferior vena cava, in the adrenal surgical bed, suggestive of pheochromocytoma. The 123I-metaiodobenzylguanidine scintigraphy/SPECT (MIBG/SPECT scan) showed abdominal uptake in the right diaphragmatic pillar. Positron emission tomography/computed tomography with Gallium 68-labeled-somatostatin-analogues (68Ga-DOTANOC PET/CT) imaging [figure 2] showed a nodular lesion with high expression of somatostatin receptors at the retroperitoneal level, located between the right diaphragmatic pillar and the inferior vena cava (with a maximum SUV of 17.6). Two months later, the magnetic resonance imaging (MRI) documented an enlargement of the right retroperitoneal lesion to 50x20mm. Laparotomy was performed after pharmacological alpha blockade with phenoxybenzamine 10mg/day. The histopathological results showed a low grade GIST, with spindled pattern, with 17 mm. Immunohistochemical staining showed positivity for CD17, CD34, S100+/-, and negativity for AE1/AE3, CAM5,2, EMA, Actin, Desmine and STAT6. There was no evidence of necrosis or lymph-node metastasis.
Discussion/Conclusion: The coexistence of bilateral pheochromocytoma and GIST is very rare.[3-5] The interesting finding in our case was the presence of a retroperitoneal lesion mimicking a pheochromocytoma in the nuclear medicine imaging. GIST lesions can express type 2 somatostatin receptors so it is important to consider GIST in the differential diagnosis of abdominal lesions in patients with NF1 even if they are asymptomatic.[4,5]

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EP-21 - INFLIXIMAB AS A THERAPEUTIC OPTION IN HYPOTHALAMIC AND PITUITARY'S SARCOIDOSIS – A CASE REPORT

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Aim: To understand the role of infliximab in the course of hypothalamic and pituitary's (HP) sarcoidosis.
Background/Methods: Neurosarcoidosis is defined by central or peripheral nervous system involvement of sarcoidosis, being associated with a worse prognosis. Although glucocorticoids are a mainstay of treatment, doses required to achieve an optimal response can be prohibitive due to disease severity and side effects. Steroid-sparing immunosuppressive therapies are also used. Infliximab has emerged as a treatment option, including in refractory and steroid-dependent patients.
A case report of a patient followed in the Endocrinology department due to HP sarcoidosis is presented. Clinical, imaging and laboratory data were collected.
Results: A female patient with 28y developed polydipsia and polyuria, with accentuated nocturia. The investigation showed low urinary density and enlargement of the pituitary gland, pituitary stalk and infundibulum on the MRI scan. Central diabetes *insipidus* (DI) diagnose was set and the patient started desmopressine. To perform etiological investigation, a chest CT was made and revealed alterations compatible with histiocytosis, starting therapy with prednisolone 40 mg daily. The situation worsened over the course of the following two years: the patient developed panhypopituitarism and the MRI showed a more pronounced stalk size. Further investigation culminated in lung and mediastinal biopsy which demonstrated evidence for sarcoidosis rather than histiocytosis. The patient continued the treatment with steroids and pituitary replacement therapy, but two years later the pituitary lesion progressed, reaching the hypothalamus region. This poor response led to introduction of intravenous infusion of infliximab (5 mg/kg/body weight) given at weeks 0.2 and 6 (loading doses) and then every 4 week (maintenance dose). After 6 months, MRI showed considerable improvements with overall decrease in the lesions' dimensions. Currently, patient is under monthly administration of infliximab, with MRI scan every 6 months and multidisciplinary monitoring. She presents either stabilization or improvement of the HP lesion after 4 years of infliximab.
Conclusion: The diagnosis of neurosarcoidosis can be challenging since the disease may mimic other conditions. First clinical presentation was central DI, that has been described as the most frequently reported endocrine disorder of neurosarcoidosis. Panhypopituitarism occurred two years later and has remained throughout the follow-up. This patient presented a poor response to glucocorticoids and the benefit of infliximab was considerable, mostly in imaging lesions. Literature shows that although MRI scans improve, most endocrine defects are irreversible. Increasing evidence suggests that the use of infliximab in neurosarcoidosis is associated with marked clinical and imaging improvements.

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EP-22 - PITUITARY APOPLEXY IN AN AIP MUTATION-POSITIVE PATIENT WITH SOMATOTROPHINOMA

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Background: While the majority of pituitary adenomas (PA) arise sporadically without a known inheritable predisposing mutation, in around 5% they can occur in a familial setting, either isolated [familial isolated pituitary adenoma (FIPA)] or as part of a syndrome. Inactivating mutations in the aryl hydrocarbon receptor-interacting protein (*AIP*) gene can be detected in 15–30% of FIPA families. Moreover, pituitary apoplexy is a relatively rare event, but occurs more commonly in individuals with *AIP* mutation-positive than those with mutation-negative tumors, although the mechanism for this is unclear.
Case Report: A 23-years-old male patient, with major depression with two previous suicide attempts by drug overdose, presented to the emergency department (ED) with a history of frequent and severe headaches, without visual changes. He was admitted to the hospital. In the study of headaches, an MRI was performed showing a 20.0x18.0 mm tumour with suprasellar extension contacting the optic chiasm and evidence of bleeding in the tumor. Acral growth and prognathism were noted. Serum IGF-1 level was 2x the upper limit of normal [704 (115 - 340) ng/mL], GH level was 6.40 ng/mL and prolactin was 17.40 (4.04 - 15.20) ng/mL, whereas free T4, TSH, cortisol and electrolyte levels were within the normal range. There was no known family history of pituitary adenoma. The nadir postglucose GH level was 5.82 ng/mL. A diagnosis of acromegaly was made and he was proposed for transsphenoidal surgery. In the meantime, he presented to the ED with refractory headache with 2 days of evolution, visual changes and ptosis. MRI showed a 24.0x21.5x26.0 mm tumor with suprasellar and cavernous extension and acute bleeding in the tumor. The patient underwent transsphenoidal surgery and histopathology showed a PA with frequent immunoreactive cells for GH and rarer for prolactin and with areas of recent and old intratumoral haemorrhage, suggestive of pituitary apoplexy. Genetic analysis revealed an AIP mutation (c.241C>T, p.Arg81Ter) in the patient and in his asymptomatic father, who was referred for clinical, biochemical and MRI assessment.
Conclusion: This case highlights the importance of considering *AIP* mutated adenomas in younger patients, with more aggressive tumors, episodes of apoplexy and extrasellar invasion. These patients may benefit from genetic testing. Screening of carriers may allow the early detection and treatment of those with PA, with

impact on follow-up and better outcomes. Future research may elucidate the molecular routes linking *AIP* mutations with pituitary tumorigenesis, potentially leading to novel treatments.

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EP-23 - 117LU-DOTA-TATE AS A THERAPEUTIC WEAPON IN NEUROENDOCRINE TUMORS (NETS): A CASE REPORT

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Introduction: NETs arise from the diffuse neuroendocrine cell system and most frequently occur in the digestive system.[1]
Sporadic small intestinal (SI)-NENs and pancreatic NENs (Pan-NENs) are the most prevalent NENs at advanced disease stages.[1]
Given the relatively indolent behavior of a large fraction of gastroenteropancreatic neuroendocrine tumors (GEP-NETs), surgery plays a role in metastatic disease, along with somatostatine analogues (SSA) for symptom control and as first-line therapy, antiproliferative drugs (everolimus, sunitinib), chemotherapy and peptide receptor radionuclide therapy (PRRT) with ^{117}Lu-DOTA-TATE: a promising therapy in the treatment of well-differentiated GEP-NETs, accomplishing a great clinical response and being very well-tolerated.[1,2]
Case Report: In 2012, a 60 year-old man, with metabolic syndrome (hypertension, dyslipidemia, diabetes mellitus) is sent to Gastroenterology practice in the setting of an abdominal mass finding, over abdominal pain complaints, episodic flushing and diarrhea.
A diagnosis of retroperitoneal fibrosis is made after biopsy and imagiological study. The patient is submitted to an explorative laparotomy, with partial enterectomy and the diagnosis of a neuroendocrine producing tumor of the ileum (NET-G1) arises.
Laboratory workup revealed: chromogranin A =6.43 nmol/L (<6,0) and urinary 5-Hydroxyindoleacetic acid (5-HIAA) =10.8 mg/24h (2.0-9.0).
Surveillance and SSA treatment is initiated, monthly.
^{68}Ga-DOTA-NOC positron emission tomography/ computed tomography (^{68}Ga-DOTANOC-PET/CT) revealed a metastatic lesion with augmented expression of somatostatine receptors in the liver, and the patient was submitted to its removal.
The patient remained asymptomatic, without signs of progression of the disease, during follow-up.
In 2014, ^{68}Ga-DOTANOC -PET/CT reveals metastatic progression of the disease and it is decided to initiate PRRT treatment.
In 2015, he is submitted to 3 cycles of PRRT: the patient remains asymptomatic and presents normal laboratory workup and no signs of treatment toxicity.
^{68}Ga-DOTANOC -PET/CT performed 6 months after PRRT treatment show regression of the disease.
In 10/2019, ^{68}Ga-PET/CT reveals progression of the disease, laboratory workup shows an augmented chromogranin A (161.2 ng/mL; <98.1) and a new PRRT treatment is proposed.
Conclusion: The patient remained asymptomatic and without signs of disease progression for 4 years, after PRRT, showing how effective this treatment can be, with a very good safety profile and no significant side effects. Thus, PRRNT appears to be the best therapeutic option for progressive GET-NETs under SSA treatment, given the excellent relationship between effectiveness and tolerability.

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EP-24 - T2-HYPOINTENSE VS NON T2-HYPOINTENSE PITUITARY ADENOMAS IN ACROMEGALY: BASELINE CHARACTERISTICS AND SHORT-TERM FOLLOW-UP

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Aim: To compare baseline characteristics and normalization of insulin-like growth factor 1 (IGF-1) at 1-year follow-up of Growth hormone (GH)-secreting pituitary adenomas based on their T2-weighted signal intensity on diagnostic magnetic resonance imaging (MRI).
Background & Methods: T2-signal on MRI of GH-secreting pituitary adenomas is being increasingly recognized as a possible marker to predict certain tumor characteristics, including tumoral size and cavernous sinus invasion, and response to treatment.[1]
A retrospective analysis was conducted using the patients diagnosed with acromegaly and treated between February 1999 and January 2019 in our tertiary pituitary care center. Only patients with MRI at diagnosis were included. Data was collected in terms of baseline characteristics: age, sex, tumoral size, T2-signal, Knosp classification, clinical co-secretion, immunocitochemical report and first treatment (surgery, medical therapy or radiotherapy). Initial and at 1-year follow-up GH and age- and sex-adjusted IGF-1 levels were also assessed. The percentage of IGF-1 levels above the upper limit of normal (%ULN) was calculated. The selected patients were dividided in two groups: T2-hypointense and non T2-hypointense adenomas (iso and hyperintense). Statistical analysis was performed using SPSS v.22. Statistical significance was set at $p<.05$.
Results: A total of 45 patients were included. T2-hypointense adenomas represented 37.8% of the cases (n=17). These adenomas were smaller (16.8±5.7 mm *vs* 24.5±14.4 mm, $p=.044$) and invaded the cavernous sinus less frequently (0% *vs* 39.3%, $p=.004$). They were associated with higher IGF-1 levels (880.5±289.6 ng/mL *vs* 666.47±246.0 ng/mL,

p=.017) and higher IGF-1 %ULN (342.4±144.9% *vs* 252.1±104.6%, *p*=.028). There were no statistically significant differences between groups in terms of sex, age at diagnosis, clinical co-secretion, immunocitochemistry (pure GH-secreting vs mixed adenoma), prevalence of macroadenoma, initial treatment and random and nadir GH levels. At 1-year follow-up, the prevalence of IGF-1 normalization was similar between groups (47.1% *vs* 46.1%, *p*=.967).

Conclusion: T2-hypointense signal was associated with higher baseline IGF-1 levels and smaller and less invasive tumors, as previously described in the literature.[1] However, it did not lead to higher prevalence of IGF-1 normalization at 1-year follow-up, showing that acromegaly treatment response is multifactorial and complex. Nevertheless, we believe that the assessment of T2 signal intensity at diagnosis is a relevant and easy method of categorizing pituitary adenomas and potentially predict some of its characteristics.

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EP-25 - CASE SERIES OF ACROMEGALY IN A SINGLE CENTER OVER SEVEN YEARS

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Aim: The aim of this paper was to present our center's experience in the diagnosis, treatment and follow-up of patients with acromegaly.

Background & Methods: 13 patients were studied at our center between 2013 and 2019 regarding clinical and hormonal features of acromegaly. We collected data regarding pituitary hormone levels, MRI scans, complications related to acromegaly and implemented therapies (neurosurgery, radiotherapy and medical treatments).

Results: 13 patients (eight women, five men) aged 36 to 66 years (mean 50.1±13.3 years) were analyzed. Three patients were referred for high IGF-1 levels and three patients had persistent disease after neurosurgery. The remaining patients were signalized for multinodular goiter (two), obesity (one) and hypercalcemia (one). Main complaints of patients were headache (five), visual impairment (three) and amenorrhea (two). At diagnosis, IGF-1 levels were 777.4±241.6 (reference values 76-286 ng/mL) and GH levels were 20.2±27.2 (3.6-60.5 pg/mL). The remaining pituitary function was normal on all patients at diagnosis and only one patient developed secondary hypothyroidism following neurosurgery. We found a pituitary adenoma at initial MRI in all patients, with a mean size of 15.5±9.8 mm. One adenoma contacted with the optic chiasm and two extended to the lateral cavernous sinus. Complications and symptoms related to acromegaly were found with the following frequency: hypertension (nine), sleep apnea (six), type 2 diabetes (five), colorectal polyps (four), multinodular goiter (three), obesity (three), osteoporosis (one), carpal tunnel syndrome (one) and clear cell renal carcinoma (one). 10 patients had already underwent neurosurgery, of which three were cured (normal IGF-1 and GH<1 pg/mL). Of the seven patients with persistent disease following neurosurgery, one received radiotherapy (gamma knife) and had normal IGF-1; the remaining six patients were under somatostatin analogues.

Conclusion: Acromegaly may still be underdiagnosed, in spite of better lab and imaging techniques. Surgical treatment is not always curative and complementary therapies, like radiotherapy and somatostatin analogues, are important to maintain normal levels of GH and IGF-1 and to prevent complications related to long standing non-controlled acromegaly.

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EP-26 - HYPOPITUITARISM - CASE SERIES OF A TREATMENT CENTER

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Aim: The aim of this paper was to present our center's experience in the diagnosis, treatment and follow-up of patients with hypopituitarism.

Background & Methods: We revised the clinical reports of all patients admitted at our center with the diagnosis of hypopituitarism between 2012 and 2019. Data regarding clinical and biochemical diagnosis, pituitary MRI and treatment were collected.

Results: 12 patients had at least one pituitary hormone deficit. Males predominate (75%) and the medium age was 57.9±20.6 years (3 to 77 years-old) at diagnosis. Nine patients were asymptomatic, and diagnosis was established after routine lab analysis or because of pituitary incidentaloma investigation. Two patients presented with diabetes insipidus and one patient had severe headache and visual impairment due to pituitary apoplexy. All patients had central adrenal insufficiency and were under therapy with hydrocortisone (mean dosage 17.7±7.1 mg/day). Diagnosis was established by morning serum cortisol, which was <3 µg/dL in 10 patients. In the remaining two patients, diagnosis was confirmed by corticotropin stimulation test. Secondary hypothyroidism was confirmed in 11 patients by TSH and FT4 analysis (mean FT4 8.05±3.86 pmol/L) and treatment consisted of levothyroxine (mean dosage 92.7±37.4 µg/day). Only 10 symptomatic patients were evaluated for hypogonadism (nine men). The diagnosis was confirmed in all of them (mean LH 0.85±0.84 mU/mL and total testosterone was bellow reference range) and therapy consisted of intramuscular testosterone injection (mean dosage 312.5 mg/month). Two patients presented initially with symptoms of diabetes insipidus and diagnosis was confirmed by water deprivation test. They received therapy with DDVAP. The only child in our series was diagnosed with hypopituitarism at three years-old and was the only one to have GH deficiency and received GH replacement therapy since childhood. Pituitary imaging was performed in all patients in order to establish the cause of hypopituitarism. Two patients presented with empty sella, one patient had pituitary stalk interruption and one patient was diagnosed with pituitary apoplexy. MRI revealed pituitary adenomas in six patients, of which three developed hypopituitarism after pituitary surgery. In two patients there were no anatomical abnormalities of the hypothalamic-pituitary region.

Conclusion: Patients with hypopituitarism may be asymptomatic, particularly when hormonal deficits develop slowly, frequently in relation to pituitary adenoma. Thus, pituitary imaging is mandatory. Some patients are diagnosed after investigation of pituitary

incidentaloma and routine thyroid function tests. Standard hormonal assays and dynamic function tests are critical for establishing the diagnosis. Hormone replacement therapy has shown to improve quality of life and reduce morbidity.

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EP-27 - RATHKE'S CLEFT CYSTS: SURGERY VERSUS OBSERVATION – COMPARATIVE ANALYSIS IN A TERTIARY PITUITARY CARE CENTER

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Aim: Characterize a series of patients with presumed Rathke's cleft cysts (RCCs) managed with surgery versus observation and evaluate their clinical, laboratorial and imagiologic outcomes.
Background & Methods: RCCs are common benign cystic sellar and/or suprasellar lesions. They are often incidentally detected and their management remains controversial, particularly when asymptomatic.1 We present a retrospective study including all patients with MRI-based RCC diagnosis from January 2002 to June 2020, followed in a tertiary pituitary care center, with at least one follow-up MRI. Patients with pars intermedia cysts or concomitant sellar lesions were excluded. The final sample was divided into observational and surgical cohorts based on proposed treatment modality.
Results: We included 33 patients (mean age at diagnosis 40.52±15.76 years; median follow-up period 59 (41-104.5) months; 72.7% female). RCC diagnosis was established during headache investigation in 53.1% of cases. High or isointense cysts on T1-weighted MRI images were found in 84.4% of patients, and peripheral enhancement rim in 75.8%. Lesions were located in sellar region with suprasellar extension in 54.5% (n=18). Transsphenoidal cyst fenestration was performed in 6 patients (18.2%). When compared to the surgical group, patients treated conservatively had more incidentally-discovered RCCs (80.8% *vs* 16.7%, p=0.006), were mainly female (81.5% *vs* 33.3%, p=0.034) and presented with lower rates of endocrinopathy (14.8% *vs* 83.3%, p=0.003), with no differences regarding age, headache or visual dysfunction. Free T4, LH, FSH and IGF-1 levels at diagnosis were significantly lower in patients who underwent surgery. Maximal cyst dimension was higher in the surgical cohort (26.5 (22-30) *vs* 10 (9-14) mm, p<0.001). Concerning headache, visual and endocrine related improvement/resolution during follow-up, there was no significant differences between treatment groups. Two patients recovered from hypocortisolism postoperatively. One patient needed reoperation 10 years later due to cyst recurrence. Among subjects in the observation cohort with follow-up, we found stable cyst size in 74.1% (n=20), reduction in 18.5% (n=5), spontaneous involution in 3.7% (n=1) and modest growth in 3.7% (n=1). All surgically managed patients had ultimate lesion shrinkage or resolution, as opposed to conservative group (100% *vs* 22.2%, p=0.002).
Conclusion: In our series, most RCC patients were managed conservatively and showed low risk of progression over time; surgical candidates were predominantly male, with larger non-incidentally discovered lesions associated with endocrine disfunction.

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EP-28 - CENTRAL DIABETES INSIPIDUS AS FIRST CLINICAL PRESENTATION OF ERDHEIM-CHESTER DISEASE

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Aim: Presentation of a clinical case of a rare infiltrative disease whose first presentation was related to pituitary involvement.
Background & Methods: Erdheim-Chester disease (ECD) is an aggressive form of non-Langerhans histiocytosis with fewer than 1000 cases reported. At the time of the diagnosis most patients have bony involvement however as ECD is an infiltrative disease it can affect any organ or system, and the vast majority also have at least one extraosseous site of involvement. Pituitary gland affection is described in about 22% of cases, with central diabetes insipidus (DI) being the most common among endocrine abnormalities. Regardless of other therapies, central DI should be properly managed but typically persist, even after radiographic regression of the disease. In patients with EDC a long term follow up is crucial because of the risk of disease progression, being the prognosis relatively poor, especially in cases of neurological and cardiovascular involvement.
Results: We report the case of a 47-year-ol woman presenting a form of ECD revealed in first instance by DI diagnosed at 24 years old. DI was rightly approached with desmopressin 0.12 mg per os (one tablet in the morning and two tablets at bedtime) obtaining reduced nocturia and partial control of the diuresis during the day, without hyponatremia. After exclusion of common etiologies DI was labeled as idiopathic. Only 3 years later, through the development of bilateral ankle pain, the diagnosis of EDC was suspected and confirmed. She was followed in the haemato-oncology unit of a reference treatment center. During her follow-up also developed neurological complains and was recently put on Pegylated Interferon alpha at high dose.
Conclusion: Because of the heterogeneity of EDC clinical presentation, the diagnosis is often challenging and delayed. Although DI used to appear early in the course of the disease, in this particular case it constituted de only symptom for almost 3 years. The evaluation of patients with DI could be challenging and the clinician should be aware of the range of etiologies that can cause the disease. The presence of bone pain was an alerting symptom that was promptly recognized and insured the diagnosis and specialized approach.

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EP-29 - UNRAVELLING THE SIGNIFICANCE OF ATYPICAL PARATHYROID ADENOMAS: HOW SHOULD WE MANAGE THEM?

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Introduction: Atypical parathyroid adenomas embody a challenge for the differential diagnosis with parathyroid carcinomas, as they display some atypical histological features, representing a group of intermediate form of parathyroid neoplasms of uncertain malignant potential. With the following case, we intend to highlight the main aspects related to the diagnosis and approach of this rare entity.

Case Report: A 74-year-old asymptomatic man was admitted to our department with a previous history of unilateral thyroid nodule. Neck ultrasound demonstrated a hypoechoic lesion with 16cm in the right lobe but no findings suggesting parathyroid adenoma were detected. Fine-needle aspiration was performed in the referred lesion, presenting a result of follicular lesion of undetermined significance (FLUS) in two sequential procedures. Analytics: TSH 1.08 µUI/mL (0.38–5.33), fT4 8.1 pmol/L (7.9–14.4), Anti-TPO Ab 9.3 IU/mL (1.0- 16.0), Anti-Tg Ab <5.0 IU/mL (5.0–100.0). The physical examination showed no abnormal findings, except a 1 cm sized mass palpable on the right thyroid lobe. Later on, the patient underwent right lobectomy. The histological examination revealed on the right lobe, a 15 cm area consisting of compact clusters of parathyroid cells with no evidence of atypia or nuclear pleomorphism, separated by thick irregular areas of fibrous connective tissue. The lesion boundaries were irregular, with no invasion of the thyroid tissue and cell proliferation index was <1%, aspects that were compatible with atypical parathyroid adenoma (WHO criteria, 2017).[1]

The post-operative analytic workup revealed TSH 1.6 µIU/mL, fT4 10.9 pmol/L, PTH 59.1 pg/mL (12.0–88.0), calcium 2.35 mmol/L (2.2-2.55), 25(OH)D 14.37 ng/mL; ACTH 49.7 pg/mL (7.2-63.3), cortisol 15.0 µg/dL (6.7-22.6), prolactin 4.3 ng/mL (2.6-13.1), IGF1 155 µg/L (35.1-216), gastrin 26 ng/L (13-115) and urinary catecholamines and metanephrines within the reference limits. Finally, neck ultrasound demonstrated left thyroid lobe without structural anomalies and absence of adenopathies. Patient was then referred for additional genetic screening and programmed regular clinical re-evaluation.

Conclusion: Atypical parathyroid adenomas are a controversial entity. Clinically, they tend to pursue a benign clinical course however there aren't specific signs. Although not available in our centre, once the histopathological diagnosis has been confirmed, parafibromin immunohistochemistry should be carried out, together with the germline testing of CDC73 gene, as recommended by some authors. No specific orientations for the surveillance of patients after parathyroid surgery exist so far however, it is recommended a close follow-up for the risk, although low, of recurrence, irrespective of the results of immunostaining.[2]

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EP-30 - PITUITARY APOPLEXY - CLINICAL FEATURES, MANAGEMENT AND OUTCOMES

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Background: Pituitary apoplexy is a rare clinical syndrome due to abrupt hemorrhaging and/or infarction of the pituitary gland. The outcome of acute pituitary apoplexy is variable and difficult to predict. This explains why the optimal management remains controversial.

Aim: To evaluate the clinical presentation, therapeutic management and outcomes in patients with pituitary apoplexy.

Methods: Retrospective analysis of patients diagnosed with pituitary apoplexy, followed at our hospital between 2005 and 2020.

Results: We identified 46 patients with pituitary apoplexy, of whom 26 were male. The median age at presentation was 52.2 years (IQR 18-88 years). The average duration of follow-up was 9.5 years. Pituitary apoplexy was the first presentation of pituitary disease in 71.7% of patients and predisposing factors were identified in 29 patients.

Headache was the most frequent presenting symptom, occurring in 43 patients (93.5%). Visual abnormalities were present in 32 patients, including ophthalmoparesis (n=16), decreased visual acuity (n=14) and visual field defects (n=18). The vast majority of patients presenting with pituitary apoplexy had macroadenoma, with a median maximal diameter of 20.5 mm. Non-functioning pituitary adenoma was the most common tumor (n=28), followed by prolactinoma (n=12). Ki67 was difficult to assess in the majority of histopathological samples due to haemorrhage/ necrosis, however, in ten samples available, the median of Ki67 was 3.3%.

At presentation, corticotropic deficiency was confirmed in 32 patients (69.6%) and thyrotropic deficiency in 31 (67.4%). Twenty-one patients underwent surgery, nineteen because of visual defects and two due to deteriorating level of consciousness. Of these patients, 17 had some visual improvement and 1 recovered the pituitary function. In the conservatively treated patients (n=25), 11 had some visual defects improvement and none of these recovered

the pituitary function. At the last follow-up, 76.1% (n=35) of patients required some hormonal replacement, including 18 patients submitted to surgery and 17 treated conservatively. Regrowth of adenoma was seen in 2 patients.
In our series, there was not statistic difference between patients treated with surgery and patients managed conservatively in the ophthalmological (p=0.277) and pituitary function (p=0.325) outcomes.
Conclusion: The epidemiological characteristics of pituitary apoplexy in this study are in line with the literature. In our study more than half of the patients remained on long-term replacement therapy, irrespective of the treatment.

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EP-31 - CHARACTERIZATION OF DOPAMINE AGONISTS-RESISTANT PROLACTINOMAS: A STUDY IN A PORTUGUESE TERTIARY CENTRE

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Background: Dopamine agonists (DA) are the first-line therapy of prolactinomas and are usually very effective to achieve normal prolactin levels, reduce tumor size and restore the gonadal function.[1,2] However, a minority of these patients do not respond sufficiently to these agents.[1-3]
Aim: To describe the prevalence of DA-resistant prolactinomas, its characteristics as well as its management in our clinic.
Methods: Retrospective observational study including patients with prolactinoma followed-up between October 2016 and December 2019. Resistance to DA was defined as the failure to achieve prolactin normalization and/or a tumor size reduction of ≥50% in a coronal surface after a minimum period of 3 months of receiving a weekly dose of 3 mg of cabergoline or a daily dose of 15 mg of bromocriptine.[2-3]
Results: We included a total of 152 patients with prolactinomas (62.5% females). The majority (n=101;66.4%) had a macroadenoma. DA-resistant prolactinomas were identified in 14 (9.2%) patients of whom 57.1% were females. At diagnosis, in this subgroup of lesions, compared with non-resistant adenomas, there was a slightly higher proportion of macroprolactinomas (85.7% *vs* 64.5%, *p*=0.091), the median baseline prolactin level was much higher (965.8 ng/mL [IQR:268.1-2576] *vs* 215.2 ng/mL [IQR:103.1-985.9], *p*=0.035) and patients tended to be younger (median age of 29.5 years [IQR:23-50.75] *vs* 40.5 years [IQR:29-49], *p*=0.068). The symptoms present at onset were sexual dysfunction (83.3%), menstrual disturbance (62.5%), visual impairment (35.7%), galactorrhea (21.4%) and headaches (14.3%). Of the 13 cases with initial analytical evaluation available, 6 patients (46.2%) had hypogonadism and 2 (15.4%) central hypothyroidism.
The first-line therapy was bromocriptine in 57.1%, cabergoline in 35.7% and surgery with radiotherapy in 7.1%. After confirmation of resistence, 42.9% switched from another DA, 28.6% underwent surgery, 28.6% mantained the same treatment, 14.3% increased to maximal tolerable doses of DA and 7.1% did radiotherapy. The causes of resistance were a failure of prolactin normalization (n=3; 21.4%), a tumor size reduction of <50% (n=1;7.1%) and absence of both hormonal and tumoral response (n=10;71.4%). Overall, resistance to bromocriptine was established 12 patients (13.6%), and to cabergoline in 5 (5.7%). At the end of the follow-up, only 1 patient became responsive to DA and hormonal disfunctions increased: hypogonadism in 7 (50%), hypothyroidism in 4 (28.6%) and hypocortisolism in 2 (14.3%).
Conclusion: The rate of DA-resistant prolactinoma of our study was similar with the published data (5%-30%).[1-4] These patients seemed to be younger, had higher prolactin levels at diagnosis, and a worst response to bromocriptine. In these cases, an alternative medical therapy should be considered.[5] A lack of a consensual definition for resistance in the literature limit the interpretation of these results.

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EP-32 - CHALLENGES IN INSULINOMA PREOPERATIVE LOCALIZATION – EXPERIENCE OF A TERTIARY CARE CENTRE

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Introduction: Insulinomas are rare pancreatic neuroendocrine tumours (pNET) which secrete insulin. About 90% are single, benign and sporadic. Due to the frequently small size, insulinomas are difficult to localize. However, preoperative tumour localization increases the chance of pancreas-preserving surgery. The present study describes the experience of a tertiary care centre in the diagnostic approach to patients with insulinomas.
Methods: We conducted a retrospective study on patients with insulinoma, followed at our centre, diagnosed between 1986 and 2020. We collected data regarding clinical presentation, biochemi-

cal confirmation of hyperinsulinism, localization methods and association with genetic syndromes.

Results: We included 23 patients (60.9% females), with median age at diagnosis of 68 years old (range 25-89). In 82.6% of patients, the clinical presentation was hypoglycaemia; in one case, insulinoma was diagnosed after liver metastases; in three cases, patients had previously diagnosed MEN1 syndrome and insulinomas were detected by routine surveillance.

Biochemical hyperinsulinism was confirmed through spontaneous hypoglycaemia in 13 patients, with mean glucose 32.9±8.5 mg/dL, insulin 23.4±17.9 µU/mL and C peptide 5.8±4.0 ng/mL. Seven patients were submitted to prolonged fasting test, achieving a mean glucose of 34.7±7.6 mg/dL, insulin 16.8±11.3 µU/mL and C peptide 3.8±2.0 ng/mL. The three patients with MEN1 did not have biochemically significant hypoglycaemia.

Anatomical localization of insulinoma required at least three different exams in 8 patients (34.8%). The tumour was identified through CT in 14/23 patients, endoscopic US in 10/12, MR in 4/6 and octreoscan in 2/4. Angiography was performed in 1 patient, with correct identification of the tumour. PET/CT with 68Ga-DOTANOC was performed in 3 patients, being negative in 2 cases and identifying in 1 case two suspicious millimetric pNET. This patient was submitted to selective intraarterial calcium injection which was not conclusive and is currently waiting for surgical exploration.

Among the 19 cases with apparently sporadic insulinoma, most patients (94.7%) had one single tumour, with median size of 1.6 cm (0.6-4.0). In MEN1 patients, 1 case presented one tumour with 9cm and 2 cases presented multiple insulinomas. Head and body were the most frequent localizations. In 4 cases, insulinomas were malignant.

The correct localization with CT, endoscopic US, MR and octreoscan was not associated with tumour size. Endoscopic US and MR appeared to be less sensitive to detect insulinomas in the tail of pancreas.

Conclusion: Insulinomas were diagnosed mostly due to hypoglycaemia. In this cohort, the majority were small and single tumours and anatomical localization was difficult, requiring multiple imaging exams in 34.8% of patients.

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EP-33 - HEPATIC ARTERY EMBOLIZATION IN A PATIENT WITH MALIGNANT INSULINOMA: A CLINICAL REPORT

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Introduction: Insulinoma is a rare neuroendocrine tumor, usually benign. Malignant tumors present greater dimensions, tend to invade vascular structures and metastasize to lymph nodes or liver. Treatment of hypoglycemia in such patients is difficult and frequently fails to respond to numerous therapeutic agents, representing a demanding challenge for clinicians. Hepatic artery embolization (HAE) has been reported as a therapeutic option for liver metastases of malignant insulinoma.

Case Report: A 78 years old male presenting with weight loss and dyspepsia was referred to Gastroenterology Department in 2014. Abdominal ultrasound revealed multiple hepatic micronodules interpreted as probable hemangiomas. Concurrently, he was diagnosed with pulmonary tuberculosis delaying diagnostic approach of hepatic nodules. In December 2017, a new abdominal ultrasound revealed an increase of nodules´ dimensions. CT scan confirmed multiple large heterogenic hepatic nodules with irregular contrast fixation and revealed a pancreatic hypervascular mass (80x36 mm). Endoscopic ultrasound with biopsy of the pancreatic lesion revealed a neuroendocrine tumor (synaptophysin positive with Ki67 5%-10%). In 68Ga-DOTANOC-PET-CT high uptake was observed in the pancreatic mass, regional lymph nodes and multiple hepatic foci. He was then referred to Oncology Department and started octreotide 30 mg IM every 4 weeks in February 2019. Patient started complaining of blurred vision episodes, hypersudoresis, nausea and dizziness that reverted with food intake. Weight gain of 9 Kg ensued in the next 2 months. In April 2019, patient was referred to Endocrinology Department. 72-hour fasting test confirmed hypoglycemia after 6 hours, due to endogenous hyperinsulinism (glucose 39 mg/dL, insulin 20.2 uUI/mL and peptide C 3.4 ng/mL). He refused to maintain therapy with octreotide and started diazoxide 50 mg/day; titration up to 175 mg/day was necessary due to persistent hypoglycemia. However, symptoms of congestive heart failure appeared and hypoglycemia episodes persisted. The multidisciplinary team decided to perform HAE for hypoglycemia control (June 2019). After HAE, not only prompt resolution of hypoglycemia was achieved, with no need of any further medication, but also a slight decrease in metastases volume. Eighteen months after the procedure no new hypoglycemia was documented.

Conclusion: In this clinical report, hypoglycemia started long after the diagnosis of metastatic pancreatic neuroendocrine tumor, with octreotide and diazoxide failing to control it and HAE was successful in this regard. As the large pancreatic mass persists, it is probably poorly differentiated and the control of hypoglycemia was likely obtained due to reduction of global volume of insulin secretory cells after HAE.

EP-34 - HYPERTENSION AND METABOLIC COMORBIDITIES IN ACROMEGALY

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Aims: To analyse the prevalence of hypertension and metabolic comorbidities at diagnosis and after multimodal therapy and its relationship with biochemical indices of control in a cohort of patients with acromegaly.

Background: In 2019, the Acromegaly Consensus Group revised and updated the consensus on diagnosis and treatment of

acromegaly comorbidities. Hypertension is a major contributor to cardiovascular mortality in acromegaly and may persist despite biochemical control of acromegaly achieved with the available therapeutic interventions. Metabolic comorbidities are frequent and can influences the choice of acromegaly medical therapy.
Methods: Retrospective study of a cohort of patients with acromegaly and with data concerning hypertension, diabetes mellitus (DM) and dyslipidemia at diagnosis and after multimodal therapy at a tertiary care center.
Results: Included 60 patients with acromegaly (58.3% female), with median age at diagnosis of 48.5 (42.0-57.0) years and median diagnostic delay of 5.5 (1.0-10.0) years. Median follow-up time was 7.8 (2.8-13.4) years. The cohort was stratified according to disease activity upon last visit (LV): remission (n=19), pharmacologically controlled (n=12), active disease (n=17), insulin like growth factor (IGF)-1 discordance (n=6), and growth hormone (GH) discordance (n=6). Of the 17 patients with active disease, 6 (35.3%) had IGF-I levels ≤1.3x the upper limit of normal. The prevalence of hypertension, DM and dyslipidemia at diagnosis was 55.0%, 36.7% and 58.3%, respectively, and did not change upon the LV (55.0%, 35.0% and 56.7%). The median number of antihypertensive, antidiabetic and antidyslipidemic drugs was similar at diagnosis versus LV. Patients who achieved remission on the LV had a lower prevalence of hypertension than those without remission, although no significant difference was found (36.8% *versus* 63.2%, p= 0.093). No patient who achieved remission had DM on the LV. DM was significantly more prevalent on the LV in patients with the concomitant presence of hypertension (p=0.028) and dyslipidemia (p=0.007), but not in female sex (p=0.786) or with presence of a macroadenoma (p=0.185). DM control, as judged from glycosylated hemoglobin levels, correlated with GH and IGF1 levels at LV (r=0.594, p=0.003, and r=0.507, p=0.004, respectively).
Conclusion: Our study shows that the prevalence of hypertension and metabolic comorbidities among patients with acromegaly remains high after multimodal therapy. These findings are similar to other series and can be explained by long-term exposure to excessive GH and IGF1 levels that may result in irreversible changes in different tissues. Effective management of acromegaly comorbidities is essential through specific treatment for each comorbidity.

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EP-35 - CHARACTERIZATION OF CRANIOPHARYNGIOMA PATIENTS FOLLOWED IN AN ENDOCRINOLOGY DEPARTMENT

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Aim: To review epidemiological and clinical data of patients with craniopharyngioma diagnosis followed in an Endocrinology Department as well as their treatment, sequelae and recurrences.
Background & Methods: Craniopharyngiomas are rare, benign, intracranial epithelial tumours. They arise from Rathke´s pouch remnants, being clinically and locally aggressive. Its diagnosis is clinical and radiological with histology confirmation. Their treatment is controversial; surgery is frequent. Craniopharyngiomas are associated with multiple morbidities aside from endocrinological.
Retrospective study of patients with confirmed craniopharyngioma diagnosis followed in an Endocrinology Department. Clinical, epidemiological, endocrinological data, treatment options, sequelae and recurrences were collected from medical files.
Results: Included 33 patients (52% male). Mean age at diagnosis was 34.3±22.7 years (3-83). Most diagnoses were made in adulthood (67%). Presenting symptoms are described. In adults, the endocrinological complaints were polyuria/polydipsia (n=2), sexual dysfunction (n=2), hairy rarefaction (n=1); in paediatrics were growth failure (n=3) and impaired sexual characteristics (n=2). Tumour locations: 6% intrasellar, 42% extrasellar, 39% both, 12% information not available (INA). Third ventricle was affected in 39%, optic quiasma in 33% and 18% had hydrocephalus. Tumour had calcifications in 9% of cases, cysts in 45% and in 45% INA. The initial approach was surgery in 36% or surgery with adjuvant radiotherapy in 64%. Radiotherapy alone was not performed. Surgery approach was transcranial in 17 cases, transnasal in 7 and in 9 INA. Postoperative complications were diabetes insipidus (70%) and obesity (48%). Regarding adenopituitary hormone deficits, 45% of adults and 91% of children had ≥3 deficits (p=0.01). Visual impairment (48%) according to surgery type was: 53%/0% (transcranial/transnasal)-p=0.02. Other sequelae: metabolic (73%), vascular (27%), neurological (15%) and sleep disorders (6%). Recurrence was observed in 36% of cases (mean time after first treatment: 5±2.83years (2–11); 3 among paediatric patients, 9 among adults. Treatment in these patients was surgery (42%), radiotherapy (25%) and both (33%). Recurrences were not associated with type of surgery or initial treatment. Disease caused retirement in 21%. Regarding patients diagnosed in paediatric age (<18 years old-33%), 4 completed secondary school, 4 have a degree, 1 a professional course and 2 are studying in a professional area.
Conclusion: Despite known craniopharyngiomas related morbidities, these patients seem to be well integrated in the community. Children with craniopharyngiomas have more adenopituitary deficits, probably related to more aggressive disease. No differences were found for tumour recurrences and initial treatment option/type of surgery in the whole group.

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EP-36 - ABSCESS AFTER POSTOPERATIVE CEREBROSPINAL FLUID (CSF) FISTULA IN ENDOSCOPIC TRANSSPHENOIDAL SURGERY (TSS) OF A PITUITARY MACROADENOMA.

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Background & Methods: Pituitary adenoma is the most common sellar-based lesion. Macroadenomas usually becomes symptomatic due to mass effect or endocrinological symptoms, in which case surgical excision may be required.[1] The transsphenoidal surgery (TSS) has several advantages including low morbidity and mortality rates, low incidence of deterioration of pituitary function and of permanent diabetes insipidus and no trauma to the frontal lobes or optic chiasm.[1] Cerebrospinal fluid (CSF) leak, meningitis and diabetes insipidus are known complications following TSS. Persistent postoperative CSF leak is the leading cause of morbidity following TSS and its incidence is around 4%.[2,3]
Aim: To report an unusual surgical complication after TSS of a clinically non-functioning pituitary macroadenoma and the balance between conservative and surgical management.
Case Report: A 50-year-old male that presented with fatigue, muscle pain, gynecomastia, and lower limbs alopecia during the course of 4 months, later developing superior temporal quadrantanopia. A brain MRI raised the suspicion of a predominantly cystic pituitary macroadenoma with suprasellar extension and compression of the optic chiasm. An endoscopic TSS resection of the macroadenoma was performed and an intraoperatory iatrogenic CSF leak was identified. A continuous lumbar drainage was placed yet proved ineffective and was removed one day after surgery. During the following days the patient developed headaches, vomit, fever, prostration, elevated inflammatory parameters, hyponatremia and intermittent rhinorrhachia. A brain MRI performed 7 days after TSS revealed an infectious process in the sphenoid sinus and the sella turcica and findings of temporal and frontobasal cerebritis on the right cerebral hemisphere. Due to the clinical improvement and rhinorrhachia resolution in the following days a conservative management with IV antibiotics was preferred.
Two additional brain MRI's, performed at 12 and 20 days after surgery, revealed abscesses formation and growth over time, with no concomitant clinical deterioration, and closure of the sellar floor and anterior cranial base osseous defects due to the late healing process, considering the surgical material filling at the time of TSS.
The abscesses were subsequently drained through right pterional craniotomy 4 weeks after the first surgery. The patient remained clinically well and the imaging findings resolved at discharge, 8 weeks later the first surgery
Conclusion: Severe surgical complications after transsphenoidal endoscopic resection of sellar lesions are relatively uncommon but CSF leaks and abscess formation require special attention. The balance between of conservative or surgical management must be thought through carefully and evaluated case by case.

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Clinical

EP-37 - DIGESTIVE NEUROENDOCRINE TUMORS

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Aim: The aim of this was to review gastropancreatic tumors followed in our hospital.
Background and Methods: Neuroendocrine tumors are rare and generally asymptomatic, even if liver metastasis are already present. Their behavior is variable.
Descriptive analysis of clinical and biochemical features patients of neuroendocrine tumors (NET) followed between 2009 and 2019. Review of clinical processes. Results: A total of 29 patients were evaluated. The mean age was 67.0 ± 1.91 years (46-85), with a male predominance (65.5%). In 89.7% the primitive tumor was located in the gastrointestinal tract and in 10.3% in the pancreas. In 1 patient, the tumors were synchronous and in 2 multifocal. The median tumor size of the primitive tumor was 15.5 mm. The tumors were located in the duodenum (34.5%), stomach (31%), ileum (13.8%), pancreas (10.3%), rectum (6.9%) and colon (3.4%). At the time of diagnosis, most patients (62.1%) had symptoms and in 34.4% metastasis identified, being predominantly hepatic (90%). In 20 patients, chromogranin A (0.2-318, N <2 ng / mL) was measured. 22 patients were submitted to surgery of which 5 recurred. In tumors in which the WHO 2019 classification applies (n = 28), in 75% and in 10.7% were considered as well differentiated tumors (grade 1 and grade 2, respectively) and 13.8% as poorly differentiated neuroendocrine carcinomas (grade 3). Six patients were treated with somatostatin analogs and 5 underwent chemotherapy. The overall survival at 5 years was 82.8% and at 10 years 79.3%. The median follow-up was 44 months.
Conclusion: In our study, most patients had symptoms, contrary to what is described in the literature. All high-risk tumors (grade 3), had metastasized at the time of diagnosis.

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EP-38 - PREDICTION OF 10-YEAR OVERALL SURVIVAL IN PATIENTS WITH STAGE IV WELL-DIFFERENTIATED NEUROENDOCRINE TUMORS

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Aim: To determine the accuracy performance of the NeuroEndocrine Prognostic Score classification (NEP-Score)[1] for predicting 10-year overall survival (OS) in stage IV well-differentiated neuroendocrine tumors (WDNETs) patients.

Background & Methods: Neuroendocrine tumors (NETs) encompass an assorted group of malignancies with a worldwide increasing trend.[2] WDNETs have a highly heterogeneous clinical course, and thus prognostic scores are helpful to categorise patients with the purpose of assisting treatment choice.[3,4] Until the development of NEP-score, there was no validated score that aimed at assessing OS prognosis of stage IV WDNETs.[1]

Twenty two stage IV WDNET patients diagnosed from January 2009 to January 2019 were enrolled in our cross-sectional population-based study. Clinical data was obtained from medical records. The NEP-Score, a novel, practical, and validated prognostic tool, was used to predict 10-year OS in stage IV WDNET patients.

Three Cox proportional hazard regression models were built to examine the association between the NEP-score as a continuous or categorical variable at the start of NET diagnosis and all-cause mortality. In Model 1, the NEP-score was considered as 2 categories ("favourable or intermediate" risk vs. "poor" risk). A comparison between the "intermediate" risk group and the "poor" risk group was performed in Model 2. The "favourable" risk category was not considered on its own due to a small size bias. In Model 3, the NEP-score was used as a raw continuous variable, and hazard ratios (HR) were computed for a one-point increase. Survival time was calculated from the date at NET diagnosis and patients were considered censored on August 31st, 2020.

Results: Baseline characteristics of the 22 patients are displayed. The model 1 and 2 revealed 10% (HR 9.969; 95% confidence interval [CI] 1.975-50.314; p=0.005) and 10.6% (HR 10.620; 95% CI 8.762-84.983; p=0.01) increase in 10-year mortality risk in the "poor" risk group compared with the "favourable and intermediate" risk group and the "intermediate" risk group, respectively. The HR from model 3 was 1.015 (95% CI 1.005–1.025, p=0.006), meaning that a one-point increase in the NEP-score was associated with a statistically significant 1.5% higher 10-year mortality risk.

Conclusion: In our stage IV WDNETs population, the NEP-score was undoubtedly accurate at stratifying patients according to their 10-year OS. The NEP-score may provide an unparalleled ability to individualize treatment once stratifying scores and treatment algorithms in this specific matter remain sparse.

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EP-39 - PAN-HYPOPITUITARISM SECONDARY TO A PITUITARY ABSCESS - A CHALLENGING CLINICAL CASE

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Aim: We aim to report a clinical case of a pan-hypopituitarism secondary to a pituitary abscess.

Background & Methods: Pituitary abscess is rare and is usually identified after surgery. The manifestations are nonspecific and imaging characteristics are the same as several other pituitary lesions.

Results: Sixty-three years old, female. On 3/2016, due to severe frontal headache and fever, with imbalance at neurological examination, admitted to the Internal Medicine service. The study revealed acute pyelonephritis and the cranial CT scan performed revealed a pituitary macroadenoma. Cerebral MRI: suprasellar lesion, with 32x20x20 mm, suggestive of adenoma. Analytically: sodium 137 mmol/L; potassium 4.0 mmol/L; PCR 342.7 mg/L (<5.0); TSH 0.5 uUI/mL (0.35-4.94); freeT4 7.4 pmol/L(9.0-19.0); freeT3 2.81 pmol/L (2.60-5.70); prolactin 34.15 ng/mL (1.20-29.93); FSH 1.35 mUI/ml; LH 0.14 mUI/mL; cortisol 6.1 ug/dL (6.2-19.4); ACTH 8 pg/mL (0-46); urinary cortisol 230.9 nmol/day (11.8-485). Visual fields without changes.

The patient was again admitted in the hospital a few more times: first presenting tiredness, polydipsia and polyuria and the analytic study was compatible with secondary adrenal insufficiency, central hypothyroidism and diabetes insipidus started supplementation with levothyroxine 25 µg, methylprednisolone 4 mg/day and desmopressin, with an improvement of symptoms; And two more times due to meningitis with Cranial CT without new findings, lumbar puncture compatible with bacterial meningitis, with positive Neisseria meningitidis A antigen, completing several broad-spectrum antibiotic cycles, without improvement. The hypothesis of chemical meningitis secondary to pituitary macroadenoma was raised, antibiotics were suspended, and started dexamethasone 4 mg/day.

On 10/2016, she was admitted to the Neurosurgery department for macroadenoma endoscopic transsphenoidal surgical approach. During surgery present purulent aspect drainage. Pathological anatomy: respiratory epithelium with inflammation. Microbiological: Staphylococcus aureus MS.

One year later, cerebral MRI: occupation of the sella turcica by air. Analytically: T4L 14.7pmol/L; FSH 0.34mUI/mL; LH 0.1mUI/ml; prolactin 12.71ng/mL, normal ionogram.

At the last evaluation, she maintained pan-hipopituitarism, under hormonal supplementation.

Conclusion: This case demonstrates the difficulty of the pituitary abscess diagnostic, which is potentially fatal. In this patient, a pan-hypopituitarism secondary to a macroadenoma was assumed, which in reality corresponded to a pan-hypopituitarism secondary to a pituitary abscess.

Patients with pituitary abscess usually have diabetes insipidus, hy-

popituitarism and headache. The preoperative presence of diabetes insipidus helps in the differential diagnosis, because it is rarely a presenting feature of pituitary adenomas.
Most patients do not recover from hypopituitarism, being a hormone replacement therapy necessary. Otherwise, most patients don't require desmopressin at long term and have normal urinary output volumes after surgery.

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EP-40 - AN UPDATE ON THE ROLE OF GERMLINE GENETIC DEFECTS IN CUSHING'S DISEASE

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Introduction: Cushing's Disease (CD) may present in the setting of familial genetic syndromes. Such cases, however, go largely unrecognized, due to phenotypic variability, incomplete penetrance, and the rarity of the disease. We determined the frequency and type of germline genetic causes of CD and characterized their clinical phenotype in a large cohort of CD patients.
Methods: We studied 245 unrelated CD patients (139 females, 60.4%), referred to our Center between 1997-2018, including 230 pediatric (≤18 years at disease onset, 93.9%) and 15 adult patients (6.1%). Germline genetic causes were identified by whole exome sequencing in 184 patients and by Sanger sequencing of specific genes in 39 patients; 22 patients did not undergo genetic testing, due to low quality or insufficient DNA. When available (n=72), corticotropinoma DNA was screened for *USP8* hotspot variants using Sanger sequencing.
Results: Eighteen patients (7.3%) had positive family history: nine presented as FIPA with unknown genetic cause, eight presented as MEN1 (six had confirmed *MEN1* variants), and one had a family history of pheochromocytoma/paraganglioma and pituitary adenoma with unknown genetic cause. Among the 227 sporadic patients (92.7%), 15 (6.6%) simplex cases had putative pathogenic variants in the following genes: *CDKN1B* (n=5), *CABLES1* (n=3), *AIP* (n=1), *MEN1* (n=1), *PRKAR1A* (n=1), *SDHA* (n=1), *TP53* (n=1), *TSC2* (n=1), and *USP8* (n=1). Altogether, cases with potentially inheritable genetic causes (familial and simplex) accounted for 13.5% (33/245) of all patients. There were no statistically significant differences in age at disease onset, age at diagnosis or tumor diameter between patients with potentially inheritable genetic defects and the rest of the cohort. Somatic *USP8* hotspot mutations were found in 21.3% (13/61) of sporadic patients, but only in 9.1% (1/11) of familial and simplex (e.g. patients with a disease-associated germline defect, but no affected relatives) cases. The global frequency of *USP8* defects was 19.4% (14/72).
Conclusion: Potentially inheritable cases of CD accounted for 13.5% of the patients in our cohort; 63.6% (21/33) of them are associated with defects in genes with a known involvement in CD. Patients with germline genetic causes of CD might present as apparently sporadic cases, due variability in disease penetrance. Somatic *USP8* hotspot mutations are rare among patients with inheritable causes of CD, suggesting different drivers for tumorigenesis in each group. Identifying the genetic causes of CD should lead to a more precise genetic testing and counselling and might aid in identifying novel therapeutic targets.

EP-41 - THE IMPORTANCE OF DIFFERENTIAL DIAGNOSIS OF THE VARIOUS INTRASELLAR TUMORS – A CASE REPORT

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Aim: Case report.
Background & Methods: Imaging is essential in intracranial tumors evaluation, although it may be difficult to distinguish the various intrasellar tumors, such as chordoma, pituitary adenoma, craniopharyngioma, Rathke's cleft cyst or pituitary carcinoma.
Results: Thirty-one years old male patient previously healthy, without chronic medication. Observed due to multiple episodes of dizziness, associated with imbalance, without changes in hearing, vision or headache, with 3 months of evolution, medicated with betahistine. Cranial CT scan was performed due to the persistence of the clinical status, which revealed: a lytic lesion involving the clivus, extending to the sphenoid body, suggestive of chordoma. He was referred to the Neurosurgery department. Cerebral MRI was performed showing a space-occupying lesion occupying and expanding to the sella turcica, with approximately 33x37x46 mm, isointense on T1, and with intermediate signal in T2. Differential diagnosis based on imaging included pituitary macroadenoma or a chordoma. Pituitary biopsy showed a neuroendocrine pituitary tumor.
The patient was evaluated in the Endocrinology department, sexual dysfunction, gynecomastia, galactorrhea, and other symptoms of pituitary dysfunction were excluded. Uncharacteristic facies. Weight: 89 kg; height: 175 cm; BMI: 29 kg/m^2.

Analytical study carried out: prolactin 4700.0 ng/mL (4.04-15.2); cortisol 10.4 µg/dL (6.2-19.4); IGF-1 174 ng/mL (91-282); FSH 3.9 mUI/mL (1.5-12.4); LH 4.0 mUI/mL (1.7-8.6); total testosterone 2.27 ng/mL (1.6-7.5), TSH 1.73 µUI/mL (0.30-3.18); Free T4 0.94 ng/dL (0.61-1.12); Free T3 3.01 pg/mL (2.66-4.33).
The analytical study suggested that the lesion corresponded to a prolactin-producing macroadenoma. The pituitary biopsy was again analyzed showing pituitary tissue, despite the presence of athypical cells.
Visual fields without changes. Normal chest-abdomen-pelvic CT. Started cabergoline 0.5 mg twice a week, with good clinical response. One year after prolactin value was 29.3 ng/mL and cerebral MRI showed a slight decrease in the lesion volume. Two years after the patient was still asymptomatic, but the prolactin value was 4487.0 ng/mL. Changed to bromocriptine 10 mg and 6 months later prolactin level was 209.0 ng/mL. The patient keeps follow-up with bromocriptine titulation.
Conclusion: This case highlights the importance of differential diagnosis of skull-based tumors, given the differences in prognosis and treatment. Pituitary adenomas are usually benign and typically slow-growing neoplasms. Aggressive pituitary tumors are characterized by a rapid growth, a resistance to conventional treatments and/or early/multiple recurrences. Aggressive pituitary tumors/pituitary carcinomas nearly always evolve from pituitary macroadenomas. Once there are no morphologic criteria to distinguish locally aggressive or even markedly atypical adenomas from pituitary carcinomas when the tumor is still confined to the sella, a tight follow-up is crucial.

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EP-42 - PHEOCHROMOCYTOMA: A RETROSPECTIVE STUDY

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Aim: The purpose of this study is to attain a detailed picture regarding the spectrum, epidemiological characterization, diagnostic approach, and treatment of the patient population with the diagnosis of pheochromocytoma in one endocrinology center.
Background and Methods: A pheochromocytoma (PHEO) is a rare neuroendocrine tumor, originating from adrenomedullary chromaffin cells. This is a non-interventional analysis of the PHEO patient population of an endocrinology center during the time period comprised between January 2012 to June 2020. This study characterized epidemiological variables, clinical manifestations, laboratory, radiology and genetic exams, just as surgical approach and follow-up.
Results: A total of 13 patients were included, 7 female and 6 male patients. The age of this group of patients ranged from 19 to 76 years old. The initial clinical presentation was an adrenal incidentaloma in 9 cases, 2 patients presented with paroxysmal hypertension or tachycardia, 1 patient with hemodynamic instability during general anaesthesia induction and 1 patient presented with refractory hypertension. In 6 cases, the pheochromocytoma was located in the right adrenal gland, in 6 cases in the left adrenal gland and one case presented as a bilateral pheochromocytoma. The tumor average size was 63 mm. A total of 10 patients presented with metanephrine and normetanephrine co-secretion, 2 cases presented with isolated normetanephrine secretion and 1 case isolated metanephrine secretion. The surgical preparation was completed with doxazosine in 7 cases, calcium-channel blockers in 4 patients, fenoxibenzamine in 1 case and in 1 case no pharmacologic pre-surgical therapy was done. Nine patients were subjected to laparoscopic adrenalectomy and 4 patients were subjected to open adrenalectomy. In 1 case the tumor was malignant in nature, presenting with pulmonary metastases. Two patients completed genetic testing and no recognized pathologic mutations were identified.
Conclusion: Due to the ever-growing number of imaging exams, a large number of pheochromcytomas are diagnosed incidentally, in an early stage of the disease and with no associated symptoms. In most cases pre-surgical pharmacologic therapeutic courses were completed, and calcium-channel blockers have been increasingly used with success. A relatively limited number of PHEO associated mutations are currently recognized, and frequently genetic tests are negative, even when the presentation raises suspicion of a genetic syndrome.

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EP-43 - HEALTHCARE UTILIZATION AND COSTS AMONG PROLACTINOMA PATIENTS: A CROSS-SECTIONAL STUDY AND ANALYSIS OF DETERMINANTS

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Aim and Background: Prolactinomas are the most prevalent functioning pituitary adenomas.[1] They affect gonadal function[2] and have a major impact on health-related quality of life (HRQoL)[3] and may therefore cause substantial healthcare utilization and healthcare costs. To date, no empirical studies have reported the annual healthcare utilization and healthcare costs in patients with a prolactinoma, while scarce reports do exist for other pituitary adenomas.[4-11] Moreover, insight into the determinants of healthcare utilization and costs of prolactinoma patients is lacking. This study therefore aimed to report healthcare utilization and costs from a broad perspective, including their determinants, for prolactinoma patients.
Methods: This was a cross-sectional study of 116 adult prolactinoma patients in chronic care in a Dutch tertiary referral center. Between September 2016 and March 2017, patients completed four validated questionnaires, assessing healthcare utilization over the previous 12 months (Medical Consumption Questionnaire), bother by disease and needs for support (Leiden Bother and Needs

Questionnaire Pituitary), generic HRQoL (Short Form-36), and self-reported health status (EuroQol 5D). Healthcare costs were calculated based on the patient-reported healthcare utilization. To assess associations between disease-related characteristics and healthcare utilization (high vs. low) and costs, logistic and linear regression analyses were used, respectively, which were adjusted for potential confounders.

Results: Mean age was 52.0 years (SD 13.7) and median follow-up was 15.0 years (IQR 7.6-26.1). Fifty-three (46.5%) patients were diagnosed with a microprolactinoma, 49 (42.2%) with hypopituitarism, and 19 (16.4%) with adrenal insufficiency. Patients visited the endocrinologist (86.2%), general practitioner (37.9%), and ophthalmologist (25.0%) most frequently. Psychological care was used by 12.9% of patients and 5% were admitted to hospital. Mean annual healthcare costs were €2065 (SD 3625), mainly for pituitary-specific medication (41.7% of total costs), hospitalization (18.2%) and specialist care (15.1%). Determinants for higher healthcare utilization were greater disease bother and needs for support, lower HRQoL, elevated prolactin, and longer disease duration. Determinants for higher healthcare costs were greater disease bother and needs for support and lower HRQoL. Tumor size, hypopituitarism and adrenal insufficiency were not significantly associated with overall healthcare utilization and costs, while patients with a macroprolactinoma did have significantly higher costs for hormone replacement therapy than microprolactinoma patients.

Conclusion: Healthcare utilization and costs of prolactinoma patients are related to patient-reported HRQoL, bother by disease and needs for support. Therefore, addressing patients' HRQoL and needs is a way forward to improve efficiency of care and patients' perceived health status.

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EP-44 - THE CHALLENGES OF GIANT PITUITARY ADENOMAS – A REVIEW OF CASES

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Aim: Giant pituitary adenomas are defined as pituitary tumors with the largest diameter of 40 mm or more, and raise special diagnostic and therapeutic challenges in clinical practice. This study aimed to characterize a single center cohort of giant pituitary adenomas.

Background & Methods: Retrospective review of giant pituitary adenomas patients observed at an Endocrinology Department between June 2016 and June 2020. Giant adenomas were defined as pituitary tumors with the largest diameter of 40 mm or more.

Results: The review revealed 499 pituitary adenomas, of which 12 (2.4%) were giant adenomas. Most patients were male (83.3%), and the mean age at diagnosis was 45.5 years (range 29-69 years). The mean follow-up was 7.3 years (range 1-16 years). Pre-treatment magnetic resonance imaging demonstrated supra-sellar extension in 90.9% and sphenoid and/or cavernous sinus invasion in 81.8%. The median tumor largest diameter was 45 mm (range 40-65 mm). In all cases, tumors presented with mass effects, including headache or visual symptoms. Hypopituitarism was observed in 75% of cases. Seven cases were prolactinomas, corresponding to 4.2% of all prolactinomas. Mean prolactin (PRL) concentration at presentation was 7714.3 ug/L (range 2000.0 – 15538.0 ug/L). All but one case were treated with dopamine agonists. In 75% of cases prolactin normalized, and in all there was a variable reduction in tumor size. Three cases were somatotroph adenomas, corresponding to 3.1% of all somatotroph adenomas. Median baseline IGF1 was 2.7 times the upper limit of normality (ULN). Two patients underwent pituitary surgery, but none achieved hormonal remission. A somatostatin analog was given as first-line therapy to the third case, but with a poor response.

Conclusion: Our results are in line with the literature: in the majority of cases of giant prolactinomas, dopamine agonists allow PRL normalization and a reduction of tumor size. On the other hand, other functioning tumors, namely somatotroph adenomas, are usually uncontrolled by surgery and respond poorly to medical treatment. These results reflect the challenge giant pituitary adenomas represent and reinforce that a multidisciplinary approach is mandatory in the management of these patients.

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EP-45 - NONFUNCTIONAL PITUITARY ADENOMAS IN ELDERLY PATIENTS: SURGERY VS SURVEILLANCE

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Aim: Compare clinical, imaging and laboratorial characteristics and outcomes of nonfunctional pituitary adenomas (NFPA) in elderly patients managed with surgery versus surveillance.
Background & Methods: NFPA account for 60%-80% of adenomas in the elderly, incidence around 7%. Majority are macroadenomas, associated with visual impairment and pituitary deficits. Considering the comorbidities of older patients, concerns regarding avoiding the risks of surgery without compromising the prognosis of patients oriented to surveillance have been raised.[1] A retrospective study was conducted in a tertiary pituitary care center, in patients with NFPA, aged >65 at diagnosis, evaluated between February-December/2019. We divided into surgical (A) and surveillance (B) groups according with therapeutic management.
Results: We included 58 patients, 31/53.4% female, median age at diagnosis 71.5 (67.0-76.0) years, median follow-up period 48.0 (24.0-84.0) months. Diagnosis was incidental in 23/41.4% cases and 20/34.5% with neurologic symptoms. Any pituitary deficits were present in 25/43.1% patients and 17/29.3% had hypopituitarism. MRI revealed a macroadenoma in 54/93.1% patients, with median maximum diameter of 20.0 (14.0-30.25) mm, 44/75.9% with suprasellar extension, 31 (53.4%) with optic chiasm compression, 18/31.0% with sphenoid extension, 40/69.0% with cavernous sinus invasion.
Group A included 21/36.2% patients, group B 35/60.3% and 2 patients were not operated because of high surgical risk (group C). Group A versus group B, had a higher frequency of visual impairment (10/47.6% *vs* 2/5.7%, p=0.011), higher maximum diameter (29.4±13.5 *vs* 18.0 (12.0-25.0), p=0.004) and higher frequency of optic chiasm compression (18/78.3% *vs* 13/37.1%, p=0.003).
Regarding group A outcomes, 13/61.9% improved compressive symptoms, 21/100% had adenoma volume reduction and none improved previous pituitary deficits. Group B showed clinical, imaging and laboratorial stability in 23/65.7%, 26/86.7%, 35/100% patients, respectively. No patients experienced clinical worsening or lesion dimension increase. Group C had no clinical impairment, growing of adenoma or more pituitary deficits.
In group A clinical improvement was more frequent (p=0.044), all experienced lesion reduction/resolution (p<0.001) and observed de novo deficits/new deficits in patients with preexisting ones (3/14.3% *vs* 0%, p=0.048), comparing with group B.
Conclusion: Surgery caused improvement in compressive symptoms associated with lesion reduction/resolution and no severe complications. Patients under surveillance remained stable, even if they had surgery indication. Although conservative management rarely allows clinical improvement, it seems to be a safe therapeutic approach to selected old patients with NFPA.

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EP-46 - RESULTS OF PATIENTS WITH POSTOPERATIVE DIABETES INSIPIDUS' LONG-TERM FOLLOW-UP

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Objectives: To evaluate the course of permanent and transient postoperative diabetes insipidus (DI).
Patients and Methods: The study included 152 patients undergoing endoscopic endonasal transsphenoidal surgery aged from 18 to 65 years with median 40 [31; 52]. The follow-up period extended over 6 years for 97 patients; 55 patients (36%) had been lost to follow-up. Patients were monitored for serum electrolytes, plasma and urine osmolality, copeptin level.
Results: At discharge postoperative DI was diagnosed in 34 patients, self-limited disturbances – in 25 patients, 91 patients had no disturbances. At 6 month 27 patients had postoperative DI, 36 patients – transient and 65 had no disturbances. At 1 year 24 patients had postoperative DI, 38 – transient DI and 62 had no disturbances. Finally at the end of follow-up 15 patients had postoperative DI, 34 had transient DI and 47 did not have any disturbances. Throughout the follow-up period DI became transient in 17 patients, contrariwise in 3 patients transient DI became constant. Constant DI developed in 1 patient without disturbances by discharge, transient – in 8 patients throughout the follow-up period.
The onset was seen on the 5th median day [1; 9.5] after surgery for the permanent DI and on the 1th median day [1; 4.5] for transient DI; median for transient DI's duration was 30 days [1.5; 195].
When assessing osmolality and sodium level, serum sodium's value in patients with a transient DI was significantly higher in comparison with patients without disturbances (p=0.008). In patients with a constant and transient DI urine osmolality's value was significantly lower compared to patients without disorders (p=0.015, p=0.001) and sodium urine's value was significantly higher (p=0.005, p=0.001). When assessing the level of copeptin, there were no statistically significant differences between constant, transient DI and patients without disturbances, nor pre- and postoperative levels, but patients with a permanent central DI form had a profound decrease in its level after the intervention (10.1 [6.2; 10.9] pmol/L *vs* 5.3 [4.9, 6.2] pmol/L).
Conclusion: Blood sodium, osmolality and sodium in urine are sensitive markers for diagnosis of postoperative DI, but the diagnosis of permanent or transient postoperative DI should be specified after a long-term follow-up. The level of copeptin as a predictor of the development of the permanent form of central DI is a promising marker for further study. The onset of postoperative DI arises on the 1-5 day after surgery and rapidity of recovery varies wildly.

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EP-47 - CO-SECRETING PROLACTIN AND GROWTH HORMONE PITUITARY ADENOMAS: A REVIEW OF 4 CASES

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Introduction: Combined prolactin (PRL) and growth hormone (GH) secretion represents 5% of all pituitary tumors. Some studies suggest that these mixed tumors have earlier onset, aggressive behavior and are less likely to achieve cure.
Clinical Cases: We report 4 cases of GH and PRL-secreting pituitary adenomas. Clinical, biochemical and radiological features are presented below.

Caso	1	2	3	4
Sex	Male	Female	Male	Male
Age at diagnosis (years)	20	51	41	35
Clinical presentation	Acromegalic features	Headache, galactorrhea, extremities enlargement	Nasal congestion	Blurred vision, diplopia
Tumor size (mm) extension/invasion	18x13 extension	25x23 extension	32x21 invasion	18x16 invasion
PRL at diagnosis*	202	3000	1910	312
IGF-1 at diagnosis (x ULR)**	3.5	2.1	3.1	3.7
Treatment	Surgery; Octreotide; Cabergoline	Bromocriptine; Surgery	Bromocriptine; Octreotide	Cabergoline
Histology	**Mixed PRL** and **GH**-secreting pituitary adenoma			

* normal range 5-26 ng/dL

** ULR - upper limit of reference

Case 1 underwent pituitary surgery with persistence of the disease (IGF-1 2xULR and PRL 25 ng/dL). Octreotide 30 mg/month and cabergoline 1 mg/week were started with PRL normalization and IGF-1 partial response. A second surgery was not curative and medical therapy was restarted. Since then, he maintains normal PRL and IGF-1. Last MRI showed residual tumor.
Case 2 diagnosed as prolactinoma was treated for 3 years with bromocriptine 7.5 mg/d. Tumor size was slightly reduced and minimum PRL 244 ng/mL. Patient noticed feet enlargement and high IGF-1 confirmed acromegaly. Cure was achieved after pituitary surgery. There is no disease recurrence after 7 years.
Case 3 was treated with bromocriptine 7.5 mg/d with PRL normalization and slight IGF-1 reduction after 6 months. MRI showed smaller tumor size (32 to 20mm). Octreotide 30 mg/month was added, with unchanged tumor size and IGF-1 at the ULR. He is waiting for surgery.
Case 4 was recently observed. Considering the diagnosis of a mixed tumor with cavernous sinus invasion, cabergoline was started in order to obtain reduction of tumor and optimizing surgery. One month after, PRL was normal and MRI showed a 2 mm reduction in tumor size. At the 3rd month IGF-1 1,6xULR) and he awaits MRI reassessment.
Conclusion: There are only few reports regarding therapeutic approach of these patients. Classically the first treatment option for mixed tumors is surgical. However, dopamine agonists may have an important role not only on PRL normalization but also on reducing IGF-1 levels and tumoral size as shown on cases 3 and 4. We did not find an aggressive clinical course in our patients.

EP-48 - THYROTROPINOMAS AS A RARE CAUSE OF THYROTOXICOSIS – CASE REPORT

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Aim: To report a case of thyroid stimulating hormone (TSH) secreting pituitary adenoma and to highlight the challenges associated with its diagnosis and treatment.
Background: Thyrotropinomas are rare pituitary tumours that secrete biologically active TSH in an autonomous way. They represent 0.7%-0.94% of all pituitary adenomas and < 1% of all hyperthyroidism causes. Patients can present with symptoms and signs of hyperthyroidism or related to tumour growth or related to the increase of other co-secreted hormones. A non-supressed TSH in the presence of elevated thyroid hormones is the hallmark of the biochemical diagnosis.
Results: A 64-year-old man was referred to the endocrinology clinic because of a pituitary incidentaloma found in a computed tomography scan performed after a fall. His past medical history included human immunodeficiency virus infection treated with antiretroviral therapy, atrial fibrillation, mitral valve replacement due to severe mitral insufficiency and pulmonary hypertension. Blood tests showed high thyroid hormones with non-suppressed TSH and also high FSH and LH levels together with high total testosterone levels: TSH 4.32 mU/L (normal range 0.27-4.20), free T4 4.22 ng/dL (normal range 0.93-1.7), free T3 11.4 pg/mL (normal range 2-4.4), FSH 14 UI/L (normal range 1.5-12.4), LH 18.8 UI/L (normal range 1.7-8.6), total testosterone 820 ng/dL (normal range 180 - 758), free testosterone 10.4 pg/mL (normal range 5.60 - 19.0). TSH levels did not increase after a TRH stimulation test (Basal 2.94 mU/L; 90' 2.97 mU/L). Alpha subunit levels were increased - 6.4 IU/L (normal range <0.8). Genetic testing did not find mutations in the TRHB gene. Pituitary magnetic resonance imaging identified a pituitary lesion with 24 mm with right cavernous sinus invasion. The patient was started on antithyroid drugs and underwent transsphenoidal surgery with subtotal tumour removal. After surgery the patient returned to euthyroid state. FSH and LH levels also decreased and total testosterone is now within the normal range. The preliminary histological report showed a pituitary adenoma positive for prolactin (negative for other anterior pituitary hormones namely TSH), chromogranin A+, CAM5.2+ "dot", Ki 67 <1%, p53 <5%. A complete histological exam is pending.
Conclusion: Although rare, physicians should consider thyrotropinomas if the clinical and biochemical scenario are suggestive. First, we must exclude more frequent causes as laboratory interferences. The main differential diagnosis is thyroid hormone resistance. Diagnosis can be challenging. Other concurrent medical conditions, co-secreted hormones and the occurrence as incidentalomas can make the investigation even more difficult.

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EP-49 - BILATERAL ADRENALECTOMY IN CUSHING DISEASE: A RETROSPECTIVE MULTICENTRIC STUDY

Fernando Fonseca (Portugal)[1]; Luisa Cortez (Portugal)[1]; João Sequeira Duarte (Portugal)[2]; Ema Nobre (Portugal)[3]; Maria João Bugalho (Portugal)[3]; Maria João Ferreira (Portugal)[4]; Davide Carvalho (Portugal)[4]; Ana Agapito (Portugal)[1]

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Introduction: Transphenoidal pituitary surgery (TPS) is the primary treatment of Cushing disease (CD) aiming a cure. Different treatment options can be considered for persistent or recurrent disease: a second TPS, pituitary irradiation, medical therapy or bilateral adrenalectomy (BAD). The last one can be indicated in cases of non-compliance, partial response or adverse effects of medical therapy and in situations of severe hypercortisolism named as *catastrophic*. Permanent adrenal insufficiency, the risk of adrenal crisis and Nelson´s syndrome are the *cons* of this approach.
Objective: to review short and long term outcomes of patients treated with BAD in CD.
Methods: retrospective, multicentric study. Data were collected by the authors from medical records of each of the four centers involved.
Results: Twenty two patients (20 female), aged 14-61years (median 30y) at diagnosis of CD were submitted to BAD between 1958-2018. Adrenal surgery as *ab initio* therapy for CD was done in 7 patients, and occured between 1958 and 1985 in 6 of them. Fifteen patients were submitted to TPS as a primary treatment, in 7 occuring twice. One third (n=5) of operated patients received radiotherapy and 78.5% (n= 11) were prescribed medical therapy -metirapone alone (3) or added to ketoconazol (5), cabergoline (2) or to pasireotide (1). Failure to control and/or the severity of hypercortisolism determined BAD, which occurred 1 to 13 years after the diagnosis of CD (median 6.4y). For the whole group (n=22), non-severe complications of surgery occurred only in 3 patients. Follow-up after BAD varied between 1 and 53 y (median – 17.9 y) 3 patients were lost and 1 died. Adrenal crisis was reported as a sole episode in only 3 patients. Nelson's syndrome was observed in only 1 case.
Conclusion: BAD is considered a salvage therapy for CD when the other treatment options fail to control hypercortisolism. Permanent adrenal insufficiency, risk of adrenal crisis and Nelson's syndrome are deemed to be the cons. Albeit being small, this series has a rather long follow-up, during which adrenal crisis was 0.7 episode per 100 patient-year and Nelson´s syndrome developed in only 1 patient. No serious surgical complications were observed. In this work, BAD proved to be safe and its efficacy supports it to be used sooner, in order to avoid the serious complications of uncontrolled hypercortisolism.

EP-50 - SUSTAINED RESPONSE TO TREATMENT WITH ORAL OCTREOTIDE CAPSULES: RESULTS FROM THE OPEN-LABEL EXTENSION OF THE CHIASMA OPTIMAL STUDY

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Aim: This analysis describes long-term durability of oral octreotide capsule (OOC) treatment response for patients who continued into the open-label extension (OLE) for an additional 48 weeks after completion of the double-blind, placebo-controlled period (DPC) of CHIASMA OPTIMAL.
Background & Methods: Oral octreotide capsules, recently approved in the US, are a treatment option for patients with acromegaly previously responding to injections. OOC safety and efficacy were reported previously from the DPC phase of the phase 3 CHIASMA OPTIMAL pivotal study.[1] All patients who completed the DPC period on study drug (OOC or placebo) were eligible to enter the OLE. During the OLE, initial OOC dose was 60 mg and could be escalated or de-escalated at the site investigator discretion based on IGF-I level and/or safety and tolerability. For this analysis, maintenance of response (IGF-I ≤1.0 x ULN) was assessed using multiple imputation (MI) in patients in the OLE who completed the DPC period on study drug (OOC or placebo and did not revert to injectable somatostatin receptor ligand treatment) at the end of the OLE.
Results: Twenty patients from each of the OOC and Placebo arms enrolled in the 48-week OLE. From the OOC arm, 90% (n=18) completed the OLE (Figure). In patients receiving OOC at the end of the 36-week DPC period (n=19), mean IGF-I levels were maintained within normal limits using MI (0.92 x ULN at OLE baseline and 0.90 x ULN at the end of the OLE). Of the OOC patients who were responders at the end of the DPC (n=14), all completed the OLE and using MI, 93% maintained their response at the end of the OLE. From the placebo arm, there were n=9 patients who had completed the DPC on placebo capsules with a mean OLE baseline IGF-I of 1.09 x ULN which improved to 0.87 x ULN on

OOC at the end of the 48-weeks. No new safety concerns were noted with prolonged exposure to OOC, although the current trial was not powered to assess more rare side effects.
Conclusion: Sustained maintenance of biochemical response to OOC is durable, and the OOC safety profile is consistent with that of injectable somatostatin receptor ligands with a similar disease burden but without injection-related AEs. OOC appears to be a potentially effective and safe long-term monotherapy for patients with acromegaly previously responding to injectable SRLs.

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EP-51 - PHEOCHROMOCYTOMAS AND PARAGANGLIOMAS – A RETROSPECTIVE STUDY

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Background: Pheochromocytomas (PPCs) and paragangliomas (PGLs) are catecholamine-producing neuroendocrine tumors arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia.
Aim: To characterize clinical features, diagnosis and therapeutics of a population diagnosed with pheochromocytoma and paraganglioma.
Methods: We performed a retrospective and observational study that included all the patients with histologically proven PCC and PGL treated at our hospital between 2006 and 2019. Data were obtained from hospital records. Descriptive statistics were applied and the results are presented by the mean and standard deviation.
Results: We found 43 patients, 27 (62.7%) had PCC and 16 (37.2%) had PGL. Referring to PCC, 21 (77.8%) patients were female, age at diagnosis was 58.7±17.4 years and mean tumor diameter was 6.2cm (range 0.6-15 cm). Right and left gland were equally affected and there was one case of bilateral PCC. Clinical presentation was: 44.4% incidentalomas, 25.9% persistent hypertension, 22.2% typical paroxysms, 3.7% abdominal pain, 3.7% hypertensive crisis. The diagnosis was confirmed biochemically in 24 (88.9%) patients. The localization was by CT in 73.3%, MIBG scintigraphy in 53.8% and MR in 23.1%. Twenty-six patients underwent adrenalectomy, of which 21 patients underwent laparoscopic adrenalectomy. One patient was diagnosed as malignant PCC due to pathologically proved metastasis and died before surgery. In 2 patients a genetic syndrome was found. There were no recurrent tumors.
Referring to PGL, 12(75%) patients were female, age at diagnosis was 53.7±12 years and mean tumor diameter was 5.6 cm (range 2-14.2 cm). The locations included head and neck (5), abdomen (5), mediastinum (3), retroperitoneum (2) and sacrum (1). Ten (62.5%) were secretory PGLs. Clinical presentation was: 18.9% incidentalomas, 18.9% persistent hypertension, 12.5% typical paroxysms, 12.5% abdominal/dorsal pain, 12.5% palpable cervical mass, 12.5% dyspnoea, 6.25% facial paralysis and 6.25% diarrhea. The localization was by CT in 87.5%, MIBG scintigraphy in 31.3%, MR in 25% and upper digestive endoscopy in 6.25%. In 1 patient a genetic syndrome was found. Four patients developed recurrent tumors and two of those patients were diagnosed as malignant PGLs during follow-up.
Conclusion: In our study, these tumors, either PCCs and PGLs, were more frequent at fifth decade of life and in female gender. The majority were incidentally discovered and hypertension was the most frequent clinical manifestation. Malignancy was rare.

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EP-52 - THE END OF DAYLIGHT SAVING TIME: CAN IT IMPROVE OUR MENTAL HEALTH?

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Introduction: In September 2018, the European Commission adopted the proposal to discontinue seasonal time changes in the European Union based, among other things, on health research that links daylight saving time to the disturbance of human biorhythm. The authors elaborate a narrative literature review to identify if the end of daylight saving time can improve mental health.
Methods: PubMed database searched using the terms “circadian rhythms”, “daylight saving time”, “mental health” and “sleep deprivation”. Only research conducted in the past 10 years was considered for inclusion.
Results: Daylight saving time imposes a change in local clock time two times a year. In the spring transition is thought to lead to the relatively loss of one hour of sleep at the night, while the autumn transition is often popularized as gain one hour of sleep. The circadian rhythm regulates sleep, rest/activity and feeding via the suprachiasmatic nucleus, synchronizing various circuits in the brain, peptides and hormones in the body, important in maintaining healthy mood. Changes in circadian rhythms has been associated to low levels of melatonin, cortisol secretion and variations in mood symptom severity. The available evidence suggest that even moderate changes in the timing of the sleep-wake cycle may have profound effects on mood disorders, acute alteration like “jet lag” or seasonal affective disorder or “winter depression”.
Conclusion: Chronobiological research appears to relate daylight saving time with disruption to the human biorhythm and suggests that the effect on the human biorhythm may be more severe than previously thought. The knowledge of the chronobiology may improve the comprehension of the psychiatric disturbances and allow the adaptation of the therapeutic strategies. Some studies defend that if we want improve human health, we should not fight against our body clock and therefore we should abandon daylight saving time and return to Standard Time throughout the year.

EP-54 - A RARE CASE OF SELLAR PATHOLOGY: COINCIDING IGG4-RELATED HYPOPHYSITIS AND PITUITARY ADENOMA

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A 69-year-old man was referred to our Pituitary Service for a 3-month history of progressive right visual loss and a finding of "pituitary enlargement" on brain MRI. He reported erectile dysfunction and his medical history included asthma, DM2 and meningitis (8 years ago).

Neuro-ophthalmology review showed visual acuity 6/60, optic neuropathy, marked visual field loss with residual superonasal island in right eye, mild 6th nerve palsy. Pituitary MRI: infiltrative lesion within the fossa extending to the right over the anterior clinoid process affecting the dura related to the dorsum sellae and the optic canal and overlying the planum sphenoidale, pituitary stalk thickening and a separate well-defined 8 mm mass in the left side of the fossa (presumed microadenoma).

He had mild hyperprolactinaemia and hypogonadotropic hypogonadism; IGF-I, TSH and ACTH reserve were normal. There was no evidence of diabetes insipidus. CSF cytology suggested inflammatory process involving B- and plasma cells. PET-CT revealed intense uptake activity in two pancreatic masses and in paraaortic, aortocaval and retroperitoneal lymph nodes. EUS-biopsy of one pancreatic lesion showed evidence of fibrosis, significant excess of plasma cells and IgG and IgG4 expression. Serum IgG4 levels were also increased [9.20 g/l (0-1.3)]. IgG4-related disease was diagnosed. Prednisolone was initiated (four-week course; 30 mg with gradual tapering to 5 mg daily) leading to full recovery of his right visual field and acuity, shrinkage of the sellar and pancreatic lesions and lymph nodes, and decrease in serum IgG and IgG4 levels. The presumed microadenoma had remained unchanged.

This is an unusual case of rare sellar pathology coinciding with a pituitary adenoma. Although hypophysitis is the most common manifestation of IgG4-related disease in the sellar region, in our patient, dural involvement was also present. This case also highlights the importance of broad differential diagnosis when approaching pituitary abnormalities on imaging.

EP-55 - CLINICAL AND RADIOLOGICAL ASPECTS OF SHOULDER OSTEOARTHRITIS IN PATIENTS WITH CONTROLLED ACROMEGALY

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Background: Acromegalic arthropathy is a well-known phenomenon in patients with acromegaly, occurring in the majority of patients regardless of disease remission status. Earlier studies assessed joint symptoms and radiographic OA in hips, knees, hands and spinal joints. Shoulder joints have not previously been radiographically evaluated.

Aim: To assess the prevalence of joint symptoms and radiographic osteoarthritis (OA) in the shoulders in patients with well-controlled acromegaly.

Study design: Cross-sectional cohort study.

Methods: Self-reported shoulder joint complaints were evaluated using a standardized interview, followed by a validated questionnaire to specifically assess disability of the upper limb (Disabilities of the Arm, Shoulders and Hands (DASH) questionnaire (total score 0 – 100)), with higher scores indicating increased disability. Health-related quality of life (HR-QoL) was assessed using the Short Form-36 (SF-36), and was reported as physical and mental component scores (PCS and MCS). Radiographic OA of the glenohumeral joint was evaluated using modified Kellgren & Lawrence (KL) scores with radiographic OA defined as a KL score of ≥2. Differences between patient groups were assessed using T tests, c2 tests, or Mann-Whitney U tests. Correlation analyses were performed using Pearson's correlations. Risk factors for radiographic glenohumeral OA were assessed using a multivariate model.

Results: In total, 51 well-controlled acromegaly patients were included (56% female, mean age 64±12 years), who were in remission for a median of 18.3 years (range 7.2 – 25.4 years). Nineteen patients received current pharmacological treatment, whereas the other patients were in remission after surgery and/or radiotherapy. Nineteen patients (37.3%) reported pain of stiffness in ≥1 shoulder joint. Median total DASH score was 9 (IQR 3 – 27) (n=46), with scores ranging from 0 to 54. Radiographic glenohumeral OA was observed in 21 patients (41.2%, 13.7% unilateral, and 27.5% bilateral). Risk factors for radiographic glenohumeral OA were higher pre-treatment IGF-1 levels (OR 1.06 (1.01 – 1.12), p=0.021), and current pharmacological treatment (OR 5.01 (1.03 – 24.54), p=0.047), respectively. Moreover, radiographic glenohumeral KL scores correlated positively with DASH scores (r=0.32, p=0.03).

Conclusion: Joint symptoms and radiographic OA of the shoulder occurred frequently in patients with controlled acromegaly, significantly impairing physical QoL. Risk factors for radiographic glenohumeral OA were high pre-treatment IGF-1 levels and current pharmacological treatment, which has previously been observed

in other joints as well. Future studies should investigate adequate treatment strategies of acromegalic arthropathy.

EP-56 - HIGH-DOSE CORTICOSTEROID TREATMENT OF IMMUNOTHERAPY-INDUCED HYPOPHYSITIS: A MULTI-CENTRIC, RESTROSPECTIVE ANALYSIS

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Aim: We sought to investigate the effect of systemic high-dose corticosteroids (HDS) on immunotherapy-induced hypophysitis (IH) in a multi-centric cohort.
Background & Methods: Hypophysitis is a frequent side effect of oncologic immunotherapy. The de facto standard treatment is systemic high-dose corticosteroids (HDS), but recent studies have questioned the benefits of this treatment. Medical records of 45 patients with IH treated by specialized endocrinologists at three tertiary referral centres in Germany and the UK were retrospectively analysed. Only patients with a follow-up of ≥ 3 months were included. Pituitary function, symptoms and MRI signs of IH during the course of disease were encoded into a database. We compared the groups using chi square test with a significance threshold of 0.05.
Results: Mean follow-up of our patients (31 male, 14 female; mean age at diagnosis 61.3±13.5 years) was 23.0±15.0 months. All patients received hormone replacement in case of central hypothyroidism or adrenal insufficiency and 8 out of 22 patients with hypogonadism received sex hormones. None of the patients with hyposomatotropism received growth hormone (GH). While 33 patients did not receive specific treatment of IH, 12 (27%) were treated with HDS. The most frequently used drug for HDS was prednisolone (n=9, 40-80 mg daily). GH deficiency was significantly more frequent in the HDS group (10% *vs* 50%; p=0.004), all other pituitary axes were equally affected in both groups. Pituitary function improved (i.e. at least one pituitary axis recovered) more often with than without HDS (42% *vs* 25%), but the level of significance was not met (p=0.31). Yet, symptoms (mostly fatigue) improved more often in patients without rather than with HDS (52% *vs*. 33%; p=0.29). In both groups, an improvement of MRI findings was observed in a similar portion of patients (25% with and 28% without HDS; p=0.91). Overall, none of the differences in outcomes reached the level of significance.
Conclusion: In our cohort, the course of IH did not differ significantly in patients with and without HDS. This finding aligns with other studies that could not find relevant benefits associated with HDS treatment. Instead, an appropriate replacement of hormone deficiencies seems important.

EP-58 - PATIENTS WITH CUSHING'S SYNDROME HAVE AN EARLY CHRONOTYPE

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Patients with Cushing's syndrome have increased cortisol secretion that does not show daily rhythms. Rhythmic corticosteroids are known to synchronise the circadian clock in most cells. Thus, these patients would be predicted to show abnormal entrainment of their cellular circadian clocks. We studied the timing of behaviour in these patients. Chronotype describes the entrained phase of the (individual) circadian clock, here evaluated via timing of sleep and wakefulness. Our aim was to evaluate the chronotype of Cushing's syndrome patients – in active phase and in remission - in comparison with a population control. We used the Munich ChronoType Questionnaire (MCTQ) that estimates the chronotype based on the mid sleep on free days corrected for the "oversleep" due to sleep debt that individuals accumulate over the workweek (MidSleep on Free days sleep-corrected, MSFsc). Exclusion criteria were the use of an alarm clock on the weekend and shift workers. We collected 84 questionnaires: 12 from patients with active Cushing's syndrome (9F:3M), 47 from patients with prior Cushing's syndrome now being in remission (37F;10M) and 25 from a control cohort without hypercortisolism (18F;7M). The mean age in the three groups was respectively 47±15 y, 49±12 y and 45±13 y. We did not find significant differences in the mean sleep onset. The mean sleep offset in both work-days and working-free days was ~1,5 hours earlier in patients with Cushing's syndrome compared with patients in remission and with the controls (sleep offset in workdays: 04:52h±01:16h, 06:14h± 01:09h and 06:13h±01:07h respectively; sleep offset in work-free days 05:52h±01:42h, 07:22h±01:21h and 07:18h±01:41h respectively). The mean MSFsc was ~1 h earlier in patients with active Cushing's syndrome (02:35h±01:03h) compared with patients in remission (03:32h±01:23h) and with the control cohort (03:32h±01:09h). The mean sleep duration in both workdays and work-free days was lower in patients with active Cushing (workdays 05:35h±01:44h and work-free days 06:09h±01:58h) compared with patients in remission (06:46h±01:08h and 07:18h±01:36h) and with the controls (06:35 h±01:23h and 07:08h±01:34h). These data show that patients with active Cushing's syndrome have an early chronotype, due to an early offset. It is noteworthy that after remission they show a similar behaviour with the control population. The description of chronic short sleep has implications for the health and quality of life of patients with Cushing's syndrome.

EP-59 - IDIOPATHIC CENTRAL DIABETES INSIPIDUS IN A LARGE EUROPEAN COHORT – TIME DOES NOT REVEAL THE ETIOLOGY

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Objective: Idiopathic central diabetes insipidus (CDI) is a rare condition. This multicenter multinational study aimed to characterize patients with idiopathic CDI.
Methods: The Hypopituitarism ENEA Rare Etiologies Observational Study (HEROS) platform invited ENEA members to include patients with rare idiopathic CDI. Demographic data, hormonal results, imaging tests, medications, autoimmune diseases at baseline and during follow-up, and death were collected.
Results: 93 patients (60 females) were included, age at diagnosis was 37±20.7 years, with mean follow-up 18.7±14.3 years. Ten patients presented with headache, 5 with fever, 31 were incidentally diagnosed. Anterior pituitary hormone deficiencies included hypogonadism in 6 patients (5 females), and hypocortisolism in one. Eighteen patients had autoimmune disease including 6 with hashimoto thyroiditis. In 6 women diagnosis was related to pregnancy. Information on imaging was available for 84 patients, 40 patients had normal pituitary imaging, and 44 had pathology of the posterior pituitary or the stalk along with other pathologies of the anterior pituitary in 21 patients, empty sella (10 patients) and anterior pituitary mass (10). Visual disturbances were not reported in any patient. All patients beside one are currently treated with desmopressin, 77% of them with oral preparation. During the last 4 years of follow-up, 9 patients were diagnosed with new hypothyroidism, hypogonadism or hypocortisolism. Etiology related to CDI was diagnosed in only one patient (sarcoidosis), and two patients died during follow-up.
Conclusion: Patients with idiopathic CDI are stable on a long-term follow-up, and secondary etiology is not uncovered.

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EP-60 - PITUITARY STALK LESIONS – CHARACTERISTICS OF PATIENTS IN SINGLE CENTER LONG TERM OBSERVATION

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Background & Methods: Pituitary stalk lesions (PSL) are various changes located in the pituitary infundibulum. The underlying pathology and exact diagnosis are difficult to establish due to their unique anatomical locus. A retrospective observational analysis of 60 adult patients (34W/26M) with pituitary lesions was performed. The mean age of diagnosis was 33.8 years (SD 23.7). The etiologies were divided into 3 groups (congenital, inflammatory, neoplastic), classified as exact, probable or unknown and characterized hormonally.
Aim: To present the etiological spectrum of pituitary stalk lesions and their clinical and hormonal characteristics on the basis of long term observation in the pediatric/adult endocrinology departments of our university.
Results: The most common causes of PSL were neoplasms (20/60, 33.3%, 14W/6M); congenital malformations were detected in 17/60 (28.3%, 6W/11M), while inflammatory etiology was found in 15/60 (25.0%, 9W/6M) of patients. The exact diagnosis was established in 26/60 (43.3%) cases (16 congenital malformations, 6 adenomas, 1 pituitary cancer,
1 craniopharyngioma, 1 germinoma and 1 lymphocytic hypophysitis [LH]). The probable cause was suggested in 26/60 patients (43.3%) – 10 with the suspicion of LH, 4 with histiocytosis, 3 with a metastatic tumor from a disseminated cancer, 3 craniopharyngiomas, 1 posterior pituitary lobe ectopy, 1 prolactinoma, 1 granular cell tumor, 2 adenomas and 1 pituicytoma. The origin of 8/60 PSL (13.3%) remains unknown. During hormonal assessment the most common insufficiency concerned the gonadal axis found in 29/60 (48.3%) of patients, followed by thyroid (26/60, 43.4%), somatotropic (21/60, 35.0%) and adrenal axis (20/60, 33.3%) insufficiencies. Hyperprolactinemia was detected in 20/60 (33.3%) of patients, while diabetes insipidus was confirmed in

15/60 (25%) of cases. 45 patients presented at least 1 hormonal deficit, some of them were transient.
In clinical aspect, symptoms associated with hormonal deficits led to the initiation of diagnostic work-up in 29 patients (48.3%; including 15 patients (25.0%) with growth retardation). Neurological symptoms such as headaches, visual disturbances and seizures were seen in 13 patients (21.7%). Polydipsia and polyuria were the primary presentation in 11 cases (18.3%), while 5 cases (8.3%) had a clinical manifestation of hormone overproduction. Incidental diagnosis was seen in 2 female patients (3.3%).
Conclusion: The diagnosis, management and treatment of the pituitary stalk lesions remains challenging. Difficulties in establishing the exact diagnosis might also be related to the non-specific, transient characteristics of the symptoms and hormonal insufficiencies. Long term observations might help better the understanding of the disease and result in improvement of management.

EP-61 - CLINICAL EVALUATION OF 112 PATIENTS WITH PROLACTINOMA: WHICH CHANGES AFTER THE ENDOCRINE SOCIETY GUIDELINES?

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Background: Prolactinoma is the most frequently diagnosed functioning pituitary adenoma. The Endocrine Society guidelines (2011) provided indications for diagnosis and clinical management of patients carrying a prolactinoma.
Aim: To evaluate whether the introduction of Endocrine Society guidelines influenced and modified the diagnostic process, clinical management, treatment choices and outcome of patients followed in an out-patient setting.
Material and Methods: This is a retrospective analysis conducted on patients previously diagnosed with prolactinoma and referring to our center between 1996 and 2018. They have been divided according to the diagnosis year into group A (before 2011) and group B (after 2011). For each participant, we collected the following data: age, clinical characteristics, performed evaluations, pituitary size (micro versus macroadenoma), treatment management at diagnosis and within the first 5 years of follow-up.
Results: Microprolactinomas were diagnosed in older age patients (p=0.0510). Macroprolactin (m-PRL) was measured more frequently in B than in A group (p=0.0005). B patients reported more often persistence or worsening of symptoms after 6 months and after 1 year from the diagnosis. In B group cabergoline dosage was increased more rarely; patients carrying a macroadenoma presented only one symptom at diagnosis more frequently than A group (p=0.0161). Cabergoline dosage was always higher in B group, but it was not statistically different. Pregnancy management has been similar in both groups.
Conclusion: The Endocrine Society guidelines have only partially modified the clinical practice in our center in prolactinomas management. Indeed, also before 2011 the routine clinical management of these patients already included the indications later provided by guidelines. The main changes for patients with a microprolactinoma consisted of a more frequent evaluation of m-PRL at diagnosis; the use of a lower weekly cumulative dosage of cabergoline was registered in those patients under medical therapy at least since 2 years. For patients with a macroadenoma, we obtained a faster diagnosis. Patients outcomes did not change.

EP-62 - GA-68 DOTANOC PET UPTAKE IN NON-NEUROENDOCRINE TUMORS

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Aim: To present two cases where the positron emission tomography with Galio-68-Dotanoc (Ga68-PET) suggests a paraganglioma (PGL) and bilateral pheocromocytoma (PCC) but an unexpected disease was found.
Background & Methods: Pheochromocytomas and PGL are neuroendocrine tumors with single biological behavior, metabolic activity and expression of somatostatin receptors. The imaging of these tumors is challenging. The Ga68-PET holds proof of somatostatin receptors expression and has been widely employed due to its high sensitivity and specificity in this field.
Results: Clinical Case 1. A 69 years female with a history of hypertension presented a right mandibular mass with a slowly increase for a year, associated with occasional palpitations. The fine needle aspiration biopsy of this mass was insufficient for the diagnosis and cervical MRI identified an expansive right submandibular lesion with 36mm with salt and pepper pattern and hyperintense signal on T2-weighted suggestive of PGL. The Ga68-PET evidenced malignant lesions in the right mandibular gland and in the adrenal glands (AG). An abdominal MRI confirmed adrenal lesions (200 mm in left AG and 65 mm in right AG), suggesting PCC. The urinary metanephrines were negative and the genetic test revealed a germinal mutation in SDH-D of unknown pathological significance. She was then submitted to an *en bloc* left adrenal and renal recession and right adrenalectomy. The histology of the left nephrectomy revealed a clear cell renal cell carcinoma (RCC) with 180 mm and the left adrenal gland showed no evidence of neoplastic tissue. The right adrenal gland was affected by a RCC metastasis. Later, it was also confirmed a metastasis of RCC in the submandibular lesion. She evolved with progression of disease, starting radiotherapy due to bone metastasis and sunitinib. She died five months later.
Clinical Case 2: A 50 years male submitted to surgery 5 years before due to RCC of the left kidney. A lesion adjacent to the inferior vena cava measuring 48mm was detected in a routine CT, suggesting PGL. The Ga68-PET showed expression in this lesion. He had palpitations complaints but was normotensive, with negative urinary metanephrines. He was submitted to surgery and histology showed a RCC metastasis. Sunitinib was initiated and he actually remains under surveillance.
Conclusion: The expression of somatostatin receptors is a characteristic of neuroendocrine tumors, but it is not pathognomonic or exclusive. In the interpretation of PCC and PGL images, it is important to consider the existence of other malignant tumors which also demonstrate high uptake in Ga68-PET.

EP-63 - MALIGNANT PHEOCHROMOCYTOMA WITH MULTIPLY METASTASES (A CASE REPORT).

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Introduction: Pheochromocytoma is a rare disease with the prevalence 0.2%-0.6% in patients with hypertension in general outpatient clinics. Malignant forms account for 10%-17% of all cases with the lymph nodes, liver, and lungs being the most common site of metastasis. Metastatic spread to the bones, however, is rare. We present a very rare case of malignant pheochromocytoma with metastases in retroperitoneal lymph nodes, lungs, base of the skull, skeletal bones (with massive destruction of the skull bones, Th6 and Th12), and the cerebellar pontine region.
Case Report: A 65-year-old woman, pheochromocytoma 7x6x5.5 cm of the right adrenal gland was diagnosed in 2010. The right adrenalectomy was performed in the Central Clinical Hospital of Russian Railways-Medicine in 2011. According to the data of histological examination, it had trabecular structure, immunohistochemistry was not carried out. During the next 5 years, control examinations were not carried out. In connection with the recurrence of arterial hypertension, she turned to an endocrinologist. Examination revealed an increase in the level of metanephrine in daily urine; CT data revealed metastases in the lungs, retroperitoneal space and skeletal bones. Resection of the middle and upper lobes of the right lung was performed with video assistance. Histologically verified as pheo-metastasis. According to immunohistochemical studies in the tumor tissue of the lung and lymph nodes, the expression of chromogranin A, synaptophysin, S100 is noted. Proliferation index Ki-67 11%, PASS 6 points. A pronounced expression of SSTR2 was also revealed, taking into account this, the patient was prescribed analogs of somatostatin (octreotide), but the progression continued. From 2017 to 2019 received complex treatment (surgery, radiation therapy, radiotherapy, polychemotherapy and symptomatic therapy). Despite the therapy, the progression of the tumor process continues. Taking into account the prevalence of the tumor process in 2020, a correction of polychemotherapy was carried out, as a result of which, according to PET-CT, data were obtained in favor of achieving stabilization of the process. However, taking into account the dissimilation of the process, taking into account the intake of α- and β-blockers: doxosazin 20 mg per day, bisoprolol 20 mg per day, clinical manifestations in the form of paroxysmal arterial hypertension persist, which significantly reduces the standard of living.
Conclusion: This clinical case suggests that it is necessary to carry out treatment in specialized organizations, to timely determine the malignant potential of pheochromocytoma for this primary tumor.

EP-64 - EXPRESSION OF OCT4 IN NEUROENDOCRINE TUMOURS OF DIFFERENT LOCALISATION AND GRADE OF MALIGNANCY

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Introduction: It is known that the transcription factor Oct4 plays a decisive role in the survival of tumour cells, most often poorly differentiated tumours, which is the reason for their progression and resistance to chemotherapy. Previously, some authors have shown an intense cytoplasmic (not nuclear) expression of Oct4 in low-grade (Grade 1,2) neuroendocrine tumours (NET)*.
Aim of the Study: Was to evaluate expression of Oct4 in low-grade (G1,2,3) and high-grade large cell / small cell neuroendocrine carcinomas (LC-NEC / SC-NEC, respectively) of different localisation.
Material and Methods: Immunohistochemistry was used to study 61 NET: lung (n=14: typical n=2 and atypical carcinoids n=4, SC-NEC n=7, LC-NEC n=1), stomach (n=16: 4 LC-NEC n=4; SC-NEC n=1; G1,2 n=11), intestine (n=13, all G1: small intestine n=9, large intestine n=2, rectum n=2), pancreas (n=14, G1,2,3). Expression of Oct4 was assessed in the cytoplasm of tumor cells, in score (0-3+).
Results: The maximum expression of Oct4 (3+) was found in most highly differentiated (G1) stomach NETs (9/11), in all small intestine NETs (9/9) and 1 large intestine NET, as well as 2 typical lung carcinoids. The high expression of Oct4 was also observed in 7/18 pancreas NETs (1 case G3 3+ and other tumours G1,2 2+), and in 1 atypical carcinoid lung (3+). In the other 33/61 NETs (54%) expression of Oct4 was weak, focal or absent at all (0-1+). It was focal (1+) in LC-NEC, and it was not found in all SC-NEC (7 lung, 1 stomach), and rectum NETs. Moderate expression of Oct4 (2+) was observed in 2 of 4 atypical lung carcinoids, 1 stomach and 1 colon NETs, 7/14 NETs of the pancreas (G1-G2). Expression of Oct4 was absent (0) in all SC-NEC and rectum NETs, focal expression (1+) was detected in all other NETs including LC-NEC.
Conclusion: According to our limited data, expression of Oct4 was most specific for low-grade ECL-cells NETs of stomach and intestine as well as lung carcinoids. The high invasive potential of such low-grade NETs may be related to the functional properties of this embryonic protein. We support further investigations of the expression of Oct4 that could be used as an additional diagnostic criteria or or prognostic factor of the disease. In the future, this phenomenon can be used to develop new approaches to the treatment of advanced and metastatic NETs of these types.

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EP-65 - OLECULAR CHARACTERIZATION OF THE SOMATOSTATIN/SST SYSTEM IN CUSHING'S DISEASE: ROLE OF TRUNCATED SOMATOSTATIN RECEPTOR SST5TMD4

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Aim: The objective of this study is to gain further insight on the molecular and functional role of somatostatin receptors (SSTs) in corticotropinoma cells, focusing particularly on SST_5TMD4.
Background and Methods: Cushing's disease is the result of prolonged and excessive exposure to cortisol caused by a pituitary tumor. Treatment with somatostatin analogs (SSA), which can reduce hormone secretion and tumor growth in other pituitary tumors (e.g. somatotropinomas), is usually ineffective in corticotropinomas. Previous studies indicated that presence of the truncated SST_5TMD4 receptor variant is associated with a lack of response to SSA in acromegaly; however, its presence and functional role in corticotropinomas is still unknown. Thus, expression levels of SSTs were measured in 28 corticotropinomas and 8 normal pituitary samples. Functional assays (calcium kinetics, ACTH secretion, cell viability) were performed in response to SSA in cell cultures. Cell viability was assessed after SST_5TMD4 overexpression.
Results: A lower expression of the SST_1 / SST_2 / SST_3 receptors was observed in corticotropinomas compared to normal pituitary samples. A more detailed analysis revealed the existence of two subpopulations of corticotropinomas that differed in the presence of high levels (n = 7) or low levels (n = 17) of expression of SST_5TMD4. The 'high' population expresses all SSTs, presenting a higher expression of SST_2 / SST_3 / SST_5TMD4 compared to the 'low' subpopulation, which predominantly expresses SST5. Furthermore, SST_5TMD4 is significantly over-expressed in the 'high' population compared to normal samples. Preliminary functional studies in cell cultures derived from corticotropinomas revealed that both 'high' and 'low' corticotropinomas differentially respond to *in vitro* treatment with SSA. Finally, SST_5TMD4 overexpression increased cell viability in both populations.
Conclusion: Our data indicate that there could be two subpopulations of corticotropic tumors, one that expresses most SSTs and another that predominantly expresses SST_5, which could confer differential responsiveness to SSA. Furthermore, presence of SST_5TMD4 seems to be associated with a higher rate of cell viability in corticotropinomas. Consequently, a detailed expression profile of all the SSTs in corticotropinomas, especially SST_5 variants, could assist the prediction of response to SSA in patients with Cushing's disease.

EP-66 - OUTCOMES OF TRANSSPHENOIDAL MICROSURGERY FOR PROLACTINOMAS - A CONTEMPORARY SERIES OF 162 CASES

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Introduction: Pituitary surgery is currently experiencing a renaissance. This study is aimed at defining the contemporary role of pituitary surgery in the management of prolactinomas.
Materials and Methods: In this retrospective, single-center study, 162 patients who underwent primary microscopic transsphenoidal surgery in our department between 2006 and 2019 were evaluated. Preoperative prolactinoma size and invasiveness, previous dopamine-agonist (DA) treatment, remission rates, surgical complications and postoperative pituitary function were assessed.
Results: The number of female patientd was 114 (70.4%) and 48 male (29.6%) patients received surgical treatment. In female patients, the proportion of microprolactinomas (n=60; 52.6%) and macroadenomas (n=54; 47.4%) was similar, while in male patients, the number of macroprolactinomas predominated (n=34; 70.8%). Female patients were younger at surgery than male patients (30.5 years vs 37.0 years).
A percentage of 62.3% of patients received pre-surgical DA. Indication for surgery differed between microprolactinoma and macroprolactinoma. While patient´s wish was the most frequent indication in microprolactinoma (in 63% of cases the only indication or the indication on a pro rata basis), the indications for macroprolactinoma were variable and included intolerance or resistance to DA, progressive loss of visual function, DA-induced cerebrospinal fluid (CSF) leakage or size reduction prior to planned pregnancy.
As expected, remission rates correlated strongly with preoperative adenoma size and invasiveness. For enclosed microprolactinomas, the remission rate was 92.1%, while for enclosed macroprolactinoma, the rate was 70.4%. Remission was achieved in half of the patients with invasive microprolactinomas and a quarter of the patients with invasive macroprolactinomas. None of the patients experienced a serious surgical complication such as mortality, vascular injury or meningitis. One patient required re-surgery due to CSF leakage. Postoperative deterioration of pituitary function was only observed in one patient. Improvement of pituitary function was observed in 32% of patients with preoperative deficits.
Conclusion: Both –conservative management with dopamine-agonists and transsphenoidal surgery are effective treatment modalities for prolactinomas. High remission rates can be achieved by surgical intervention, especially in non-invasive microprolactinomas. Therefore, surgery is not only indicated for loss of vision or DA-induced CSF-leakage but also a good and secure option for young patients with small prolactinomas to avoid potentially life-long DA treatment.

EP-67 - TRENDS IN DISCORDANCE BETWEEN GH AND IGF-1 AFTER SUCCESSFUL PITUITARY SURGERY FOR ACROMEGALY

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Aim: To evaluate the impact of discrepancy between nadir growth hormone (GHn) after OGTT and age- and sex- standardized insulin-like growth factor-1 (IGF-1) (suppressed GHn and elevated IGF-1 or vice versa) over the risk of biochemical and tumour recurrence after initial surgery for acromegaly.
Background & Methods: Persistent or intermittent postoperative discordance rate between nadir GH after OGTT and IGF-1 is up to 25%[1] in patients naïve to radiation and somatostatin analogues, and remains a challenging issue in the follow-up of acromegalic patients. In this retrospective study, we included 28 patients who have been treated or were under follow-up for acromegaly in our tertiary care center from 2010 to 2020. Patients who have undergone radiotherapy or had a tumour remnant at 3 months after initial surgery or with any medical treatment for acromegaly before/at the time of objectified discrepancy and patients with factors that could possibly influence IGF1/GHn levels were excluded. A GHn cut off level of 1 ng/ml was adopted.
Results: Study group included 9 males and 19 females. At diagnosis, mean age was 42±10.6 years, and mean tumor size 11.3±7.8 mm (CT scan) or 17.9±11.8 mm (MRI scan). The mean duration of follow-up was 4.5±2.4 years. 25% had normal IGF-1 and non-suppressible GHn (1.61±0.38 ng/mL) and 75% had elevated IGF1 with suppressed GHn. During follow-up, 14 normalized IGF-1 and GH without any further treatment, with a mean period until normalization of 28 months; 9 had persistence of discordant values and no tumor recurrence on imaging during follow-up, and 5 patients presented biochemical and tumor recurrence at 15 months.
Conclusion: Out of 28 patients with discordant IGF-1 / GH levels and no imaging tumour evidence at 3 months, only 15% presented biochemical and tumour recurrence, while the majority had no recurrence disease during follow-up. Therapeutic approach should be individualized between additional medical treatment and close follow-up in biochemically discordant patient.

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EP-68 - EVOLUTION OF ADRENAL FUNCTION AFTER SURGERY IN CENTRAL OR PERIPHERAL CUSHING

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Introduction: Surgery is the first line of treatment in both Cushing's disease (CD) and Cushing syndrome (CS). Successful surgery is highly probable when patients develop adrenal failure soon. After surgical cure, most patients develop transient secondary adrenal insufficiency with a variable time of recovery. Adrenal function testing can identify patients who may require glucocorticoid replacement.
Methods: We reviewed 78 patients who were diagnosed with CD or CS between 2010-2020. Successful pituitary surgery was done in 16 CD and adrenal in 18 CS patients. Postoperatively, blood was sampled for plasma cortisol levels at 08:00 a.m. and 4 hours and 24 hours after im administration of 1 mg Synacthen depot (tetracosactide). Glucocorticoid replacement was started for basal plasma cortisol < 5 ug/dL, or a stimulated plasma cortisol < 20 ug/dL. Follow-up was performed at 3, 6, 9 months and 1 year or more in selected cases, in order to see the duration of glucocorticoid replacement, morphological aspect of the contralateral adrenal and complications remission.
Results: Between 2010-2020, 55 patients with CS were diagnosed with benign ACTH- independent CS in our clinical department, 7 men and 48 women, with a mean age of 52 years ± SD 11.68 (range 26-76): 43 adenomas and 12 bilateral macronodular hyperplasia. Tumor size ranged from 16-140 mm (medium 39 ± SD 20.2 mm). Subclinical Cushing (abnormal dexamethasone test only) was diagnosed in 29 cases and overt Cushing in 26 cases. Mixed glucocorticoid and androgen secretion was found in 4 cases. From all cases, 40 patients underwent unilateral adrenalectomy. 6 patients were excluded because of missing data. From the remaining 34 patients, 18 were with secondary adrenal insufficiency (15 with overt CS and 3 with subclinical CS), receiving glucocorticoid replacement therapy for a period of time that ranged from 3 to 18 months. The decision of ceasing therapy was based on a stimulated cortisol value ≥ 20 ug/dl. A longer period of substitution was required for those patients with atrophic contralateral adrenal at initial morphological evaluation.
Conclusion: Only about a half of the patients with autonomous secretion of glucocorticoids (with or without clinical features of CS) develop postoperatively secondary adrenal insufficiency. 1 mg Synacthen depot test is useful for the decision of starting or ceasing the replacement therapy.

EP-69 - ANALYSIS OF TP53 MUTATIONS IN FUNCTIONAL CORTICOTROPH TUMOURS

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Introduction: *TP53* (tumour protein p53) is frequently mutated in cancer. In contrast, *TP53* mutations have been rarely reported in

pituitary tumours, and those reports were confined to exceptional cases. A recent study performing exome sequencing on 18 corticotroph tumors revealed pathogenic *TP53* mutations in ~30% of cases, suggesting that they may be more frequent in macroadenomas than previously thought. Noteworthy, all *TP53* mutations were found in tumours with *USP8* wildtype status.

Aim: To determine the prevalence of *TP53* mutations in a cohort of *USP8* wildtype tumours.

Methods: We conducted a retrospective study with fresh-frozen tumour samples of 33 patients with functional corticotroph tumours (16 female, 17 male), including 31 patients with Cushing's disease and 2 with progressive corticotroph tumour growth after bilateral adrenalectomy (Nelson syndrome). All 33 tumours had *USP8* wildtype status, as determined by Sanger sequencing. Nine of them were microadenomas. *TP53* coding region was amplified by PCR and analysed using Sanger sequencing.

Results: We identified *TP53* single-nucleotide variants (SNV) in four tumours (12%). Two of them were found in the two Nelson tumours (100% vs 6.5% in CD, p=0.011). Mutations were located in exons 6 (c.644G>A;p.Ser215Asn), 7 (c.773A>C;p.Glu-258Ala), 8 (c.818G>A;p.Arg273His) and 10 (c.1009C>G;p.Arg-337Gly). No insertions or deletions were identified. All mutations appeared in heterozygosity and were predicted to be pathogenic or likely pathogenic. In contrast, *TP53* mutations were absent in an additional cohort of 12 *USP8* mutant corticotroph tumours, indicating mutual exclusivity.

No differences were found regarding age at diagnosis (*TP53*mut 54 *versus* *TP53*wt 44 years; $p>0.05$) and gender of the patient, despite the fact that *TP53* mutations were present mostly in males (17% *vs* 7%; $p>0.05$). Patients with *TP53* mutant tumours underwent more than one prior surgical intervention (median number: *TP53*mut <2 *vs* *TP53*wt 0; $p=0.014$), and were more frequently treated with radiation therapy (*TP53*mut 33% *vs* *TP53*wt 0%; $p=0.018$). All mutant tumours were macroadenomas and tended to be larger, although this did not reach statistical significance. We also observed a trend towards higher rate of invasion in the cavernous sinus (*TP53*mut 36% *vs* *TP53*wt 0%; $p=0.1$). No differences were detected in terms of hormone levels.

Conclusion: In functional corticotroph tumours TP53 mutations are not as rare events as previously considered and may be related to a more aggressive tumour behaviour.

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EP-70 - FACTORS INVOLVED IN RESPONSE TO ANTIHYPERTENSIVE DRUGS IN PHEOCHROMOCYTOMA / PARAGANGLIOMA

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Introduction: Pheochromocytomas (PCCs) and paragangliomas (PGLs) are rare, but unique tumors. They are associated with excessive catecholamine secretion that leads to high morbidity rates, even though the majority of tumors is benign. They are associated with a wider range of susceptibility genes than any other solid tumor type.

Material and Methods: We realized a retrospective study, in which we included 42 patients with PCC and PGL, aged between 21-83 years old, 32 females and 10 males, 9 of them with familial PCC: 4 with RET protooncogene mutation, 2 with *VHL* mutation, 2 with *NF1* mutation and 1 with Carney syndrome, the remaining patiens having sporadic PCC. We compared antihypertensive drugs response in patients with mutations and in those without mutation. We also correlated catecholamine levels with antihypertensive drug response and mutation type.

Results: The patients with RET mutation needed less antihypertensive drug classes (α blocker and β blocker) compared to those without mutation who needed 3 or more drug classes. Regarding the catecholamine ranges correlated to the arterial blood pressure levels and to the response to antihypertensive drugs, there is a direct association between catecholamine levels, antihypertensive drug response and mutation type. So, in patients with RET, *VHL* and *NF1* mutations catecholamine levels are lower (mean 221 pg/mL in patients with RET mutation present versus mean 491 pg/mL in those without mutation) and patients with lower levels of catecholamine have had a lower systolic blood pressure (max. 198 mmHg) (*versus* those without mutation-max. 330 mmHg) and needed less antihypertensive drugs.

Conclusion: Genetic aspects play an important role in clinical manifestations of PCC and PGL. Maybe the pathogenic mutation is associated to the polymorphisms of the same gene that predispose to a certain secretion pattern of the catecholamines and to the response to certain antihypertensive drug classes.

EP-71 - MIDPARENTAL HEIGHT IS AN IMPORTANT TOOL IN THE DIAGNOSIS OF TALL STATURE IN ACROMEGALY AND IMPROVES THE DIAGNOSIS IN WOMEN

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Introduction: Excessive tall stature (TS) is a rare manifestation of acromegaly, with higher prevalence reported for males. The aim of this study was to evaluate the relationship between body height of patients with growth hormone (GH) excess related to midparental height (MPH) and population mean body height and its association with clinical features and to test whether TS patients with acromegaly come from tall families.

Methods: This is a single-centre, observational study performed among unselected adult patients with acromegaly and no family history of pituitary adenoma. Patients were analysed in two subgroups depending on body height using country-specific data: 1. normal stature (NS) and 2. TS group, defined as either body height

above 97 percentile for sex or as >1.5 standard deviation (SD) from MPH.

Results: Twenty four percent of acromegaly patients (13 females/11 males) met either of TS criteria. TS patients were significantly younger at the diagnosis (mean±SD, 33.6±13.4 *vs* 50.6±12.3 years) and at first symptoms (median, range, 27.5 (23-42) *vs* 41 (33-54) years) with greater tumour size and higher basal GH concentration than NS patients ($p<0.01$). Use of MPH was characterized by a greater detectability of TS than abnormal body height in regard to population mean. There was no difference in body height of kindred between both groups and they were not taller than population mean. Genetic testing was performed among 15/24 TS patients.

Conclusion: One fourth of adult patients with acromegaly have TS with similar frequency in males and females. MPH improves the diagnosis of TS in women.

EP-72 - ACROMEGALY OF UNKNOWN ORIGIN COEXISTING WITH AMBIGUOUS PITUITARY LESION AND SQUAMOUS CELL LUNG CANCER IN A 74- YEAR-OLD MALE.

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Introduction: Acromegaly can be caused by an ectopic production of GH or Growth Hormone-Releasing Hormone (GHRH) by various neoplasms. In case of coexisting acromegaly symptoms and pituitary hyperplasia, suspicion of ectopic GH production should be considered. Majority of GHRH ectopy cases of pulmonary origin have been associated with carcinoid tumors.[1-3] Squamous cell carcinoma of the lung has been associated with ectopic Cushing's syndrome,[4] but secretion of GHRH by this neoplasm has not been reported so far.[5]

Case Report: The authors present a case of a 74-year-old male referred to the Department of Endocrinology due to acral enlargement, frontal bossing and enlarged tongue as well as wide spacing between the teeth developing for many years. Pituitary magnetic resonance imaging (MRI) revealed a cuneatic-shaped, hypointense focal lesion (8x7x6 mm) in the right posterior part of the anterior pituitary lobe, radiologically interpreted as either hyperplasia of the intermediate lobe or atypical adenoma. Pituitary gland was not enlarged. IGF-1 and GH concentrations were elevated and no suppression of GH secretion after oral glucose load was observed. Furthermore, the patient was diagnosed with a polycyclic tumor in the 2nd segment of the right lung. Due to clinical suspicion of ectopic secretion of GH or GHRH Ga^{68}- DOTA TATE PET/CT was performed, but no pathological accumulation of the tracer was discovered. Contrarily, 18FDG- PET/CT revealed a pathological metabolic activity within the focal lesion of the right lung. The patient underwent an upper right lobectomy, with a histopathological confirmation of the squamous cell carcinoma, non-keratinizing, G3, with a negative immunohistochemical reaction for GH. IHC for GHRH has been scheduled. One cycle of adjuvant chemotherapy (carboplatin+paclitaxel) was administered. Upon follow-up, no biochemical remission of acromegaly was observed and the pituitary MRI showed stable radiological image of the pituitary tumor, suggesting a possible metastasis to the pituitary or an atypical adenoma. The MRI also detected a probable metastatic lesion in the right cerebellar hemisphere, which was subsequently resected. Histopathologically, metastasis of the primary lung cancer was confirmed. Due to unfavorable prognosis, the patient was disqualified from neurosurgical resection of the pituitary tumor.

Conclusion: The authors report a case of acromegaly of an unidentified origin, with an ambiguous radiological image of the pituitary lesion and squamous cell lung cancer.

In unclear cases of acromegaly, ectopic production of GHRH should be taken into consideration.

EP-73 - INTRASELLAR CAVERNOUS HEMANGIOMA, A RARE CONDITION CAUSING BOTH RADIOLOGICAL AND CLINICAL DIFFICULTIES- A CASE REPORT.

Andrzej Nowak (Poland)[1]; Magdalena Godlewska (Poland)[2]; Łukasz Kluczyński (Poland)[2]; Anna Bogusławska (Poland)[2]; Damian Rogoziński (Poland)[2]; Marcin Motyka (Poland)[2]; Anna Grochowska (Poland)[3]; Dariusz Adamek (Poland)[4]; Alicja Hubalewska-Dydejczyk (Poland)[2]; Aleksandra Gilis-Januszewska (Poland)[2]

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Introduction: Intrasellar cavernous hemangiomas constitute an extremely rare group of findings in endocrinological practice.[1] Diagnosis remains challenging due to non-characteristic symptoms and neuroradiological features which may resemble those of pituitary adenomas.[2]

Case Report: We present a case of female born in 1941, diagnosed with a hemangioma cavernosum located in the sella turcica.

In 2004 our patient presented with uncharacteristic symptoms: syncopes and chronic headaches. Computed tomography (CT) of the head revealed an intrasellar hyperdense tumor mass with radiological features suggesting a pituitary adenoma.

In 2005 the patient underwent transcranial resection of the sellar mass, with subsequent oculomotor nerve palsy.

In histopathological examination, diagnosis of cavernous hemangioma was determined.

Between 2005 and 2020 patient was asymptomatic, with multiple follow-up head MRIs scans, showing gradual progression in size of the intrasellar tumor. The patient was consulted by a neurosurgeon, with no direct indications for surgical approach found. Furthermore, due to suprasellar expansion into the direct proximity of the right optic nerve, the patient was disqualified for gamma-knife radiotherapy.

The last MRI of the hypothalamic-pituitary area in 2020 revealed a polycyclic, homogeneous, 33x31x29 mm mass, filling in the space of the Sella turcica, with strong enhancement after contrast

administration. Invasion of the surrounding structures, including the clivus, right cavernous sinus and right trigeminal cave were described. Bilaterally, internal carotid arteries and right optic nerve adhered directly to the lesion. Pituitary gland was compressed by the tumor mass.
In July 2020, in order to verify the ambiguous radiological and clinical characteristics of the lesion including tumor regrowth and its invasiveness, a transsphenoidal partial resection was performed. Tissue samples were collected for the histopathological examination, which confirmed the initial diagnosis of cavernous hemangioma originating from the cavernous sinus.
During a multidisciplinary tumor board, having taken into consideration relatively stable clinical condition and high risk possible surgical complications, the patient was currently disqualified from neurosurgical re-operation nor radiotherapy. Surprisingly, during whole follow up, patients pituitary function remained unimpaired. A watchful waiting approach, with radiological and endocrinological follow up were scheduled.
Conclusion: To date, only few cases of intrasellar cavernous hemangiomas have been reported. Intrasellar hemangiomas may originate from the vascular tissue of the cavernous sinus.
Surgical removal remains the recommended treatment modality, but radiosurgery could be a therapeutic option as well.3-5 Stable patients with no clinical symptoms may remain in observation.

EP-74 - GONADOTROPH PITUITARY ADENOMAS: IS THERE A CLINICAL DIFFERENCE FROM NULL CELL ADENOMA?

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[2] *Faculty of Medicine of University of Porto*
[3] *Department of Neurosurgery of Centro Hospitalar Universitário de São João E.P.E.*
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Introduction: Non-functioning pituitary adenomas (NFPA) correspond to 25%-35% of all pituitary adenomas. Gonadotroph adenomas (GA) are 70%-90% of NFPA. Null cell adenoma (NCA) are NFPA. Surgical resection is the first-choice treatment for symptomatic patients with NFPA. Hormone *deficits* may occur following surgical treatment. NCA are considered, in general, as more aggressive than GA.
Aim: Our aim was to evaluate patients with NFPA submitted to surgery and analyze clinical differences between patients with GA and NCA.
Methods: Retrospective analysis of our pituitary adenoma database. Absence of clinical hyperesecretion and gonadotropins immunohistochemistry posistivity for GA and negativity for NA were used.
Results: One hundred twenty four patients with NFPA were submitted to surgery. A total of 36.3% (n=45) were female and the median age was 69.5 years. Pos-surgery MRI showed no progression of the disease in 55 patients (44.4%), no pituitary lesion in 9 patients (7.3%), diminished lesion in 8 (6.5%), and progression of the disease in 9 patients (7.3%). A percentage of 27.4% (n=34) needed radiotherapy. Following surgery, 70 patients (56.5%) developed hypopituitarism, most commonly panhypopituitarism (affecting adrenal, thyroid and gonadal axis) (n=25, 20.2%). Thyroid and adrenal insufficiency or gonadal and adrenal insufficiency was observed in about 11% of the patients. Thyroid and gonadal insufficiency and isolated deficits were found less often.
Sixty to two patients had GA and 30 had NCA. About 30% of the patients in each group were female and the median age was around 70. On the follow-up MRI, 5 patients with GA and 1 patient with NCA showed progression of the disease (8.1% *vs* 6.5%, *p*=). Sixteen patients with GA and 13 patients with NCA needed radiotherapy (25.8% *vs* 43.3%, *p*=).
During follow-up, 34 patients with GA and 22 patients with NCA developed hypopituitarism (54.8% *vs* 73.3%, *p*=). Panhypopituitarism (affecting thyroid, gonadal and adrenal axis) was the most common, affecting 11 patients with GA and 10 patients with NCA (27.4% and 33.3%, respectively). 7 patients with GA and 3 patients with NCA (11.3%, 23.3%) developed thyroid and adrenal insufficiency. Gonadal and adrenal insufficiency was seen in approximately 10% of the patients in both groups. Isolated hormonal *deficits* were less frequent. During follow-up 3 patients died, with complications not related to the pituitary adenoma.
Conclusion: Our study, by its retrospective nature is limited by data collection and by loss of follow-up. In our center, radiotherapy was performed more often in patients with NCA, which also develop hypopituitarism in a higher percentage. Patient's characteristic and rates of progression of disease during follow-up are similar.

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Os Editoriais são da responsabilidade do grupo editorial ou solicitados por convite do Editor-Chefe e constituirão comentários sobre tópicos actuais ou comentários sobre artigos publicados na revista. Não devem exceder as 1200 palavras, um máximo de 20 referências bibliográficas e podem conter uma tabela e uma figura. Não têm resumo.

Cartas ao Editor

As cartas ao Editor consistem em comentários críticos sobre um artigo publicado na revista ou uma nota curta sobre um determinado tópico ou caso clínico. Cartas ao Editor não devem exceder 600 palavras e 10 referências e pode conter uma figura ou tabela. Não têm resumo.

Imagens em Endocrinologia

Esta secção destina-se à publicação de imagens clínicas, radiológicas, histológicas e cirúrgicas relacionadas com casos de endocrinologia, diabetes ou metabolismo.

O título não deve ter mais de oito palavras. Os autores devem ser no máximo quatro. As imagens devem ser de alta qualidade e valor educativo. São permitidas até 4 figuras**.** As legendas devem ser breves e informativas. Setas ou outros símbolos devem ser incluídos conforme necessário para facilitar a compreensão das imagens. O texto não deve exceder 500 palavras, até cinco referências, e deve incluir uma breve história clínica e dados relevantes do exame físico, testes laboratoriais e progressão clínica, conforme apropriado. Não têm resumo.

Perspectiva

Este é o tipo de manuscrito é submetido a convite do Conselho Editorial. Pode abranger uma ampla diversidade de temas relacionados com endocrinologia, diabetes, metabolismo e saúde: problemas atuais ou emergentes, políticas de gestão e saúde, história da medicina, questões de sociedade e epidemiologia, entre outros. Um Autor que deseje propor um manuscrito nesta seção deverá enviar um resumo ao Editor-Chefe, incluindo o título e a lista de autores para avaliação. O texto não deve exceder 1200 palavras, até 10 referências, e até 2 tabelas ou 2 figuras. Não têm resumo.

Guidelines

Os guias de prática clínica não devem exceder 4000 palavras, até 6 tabelas ou figuras e até 100 referências. Resumo até 350 palavras.

Referências

I.Citação no texto

Certifique-se de que todas as referências citadas no texto também estão presentes na lista de referências (e vice-versa). As referências devem ser listadas usando algarismos árabes pela ordem em que são citados no texto.

As referências a comunicações pessoais e dados não publicados devem ser feitas diretamente no texto e não devem ser numeradas. Citação de uma referência como "in press" implica que o item tenha sido aceite para publicação. Os nomes das revistas devem ser abreviados de acordo com o estilo da Medline.

As referências a artigos publicados em revistas devem incluir o nome do primeiro autor seguido dos nomes dos restantes autores, o título do artigo, o nome da revista e o ano de publicação, volume e páginas.

Certifique-se de que os dados fornecidos nas referências estão corretos. Ao copiar referências, tenha cuidado porque já podem conter erros.

A lista de referências deve ser adicionada como parte do texto, nunca como uma nota de rodapé. Códigos específicos do programa de gestão de referências não são permitidos.

II. Formato

Uma descrição detalhada dos formatos de diferentes tipos de referência pode ser consultada em ICMJE *Recommendations* (http://www.icmje.org/recommendations/). Liste todos os autores se houver seis ou menos. *Et al* deve ser adicionado se houver mais de seis autores. Título do artigo, nome da revista, ano, volume e páginas.

III. Estilo de referência

Texto: Indicar as referências no texto por número (s) em expoente. Os autores podem ser referidos, mas o número de referência deve ser sempre dado.
Lista: Ordene as referências na lista pela ordem em que aparecem no texto
Exemplos:
Referência de artigo:

1. Isidori AM, Sbardella E, Zatelli MC, Boschetti M, Vitale G, Colao A, et al. Conventional and nuclear medicine imaging in ectopic Cushing's syndrome: a systematic review. J Clin Endocrinol Metab. 2015;100:3231-44.

Referência de livro:

2.Ware JE, Kosinski M, Dewey JE. How to score version 2 of the SF-36 Health Survey: standard & acute forms. Lincoln: Quality Metric Incorporated; 2000.

Referência de capítulo de livro:

3. Castellano Barca G, Hidalgo Vicario M, Ortega Molina M. Transtorno del comportamento alimentário. In: Castellano Barca G, Hidalgo Vicario M, Redondo Romero A, editores. Medicina de la adolescência – atención integral. 2ª ed. Madrid: Ergon; 2004. p.415-29.

Referências Web:

4. No mínimo, o URL completo deve ser dado e a data em que o documento foi consultado. Qualquer outra informação, se conhecida (nomes de autor, datas, referência a uma publicação de origem, etc.), também deve ser dada.

Notas de Rodapé

As notas de rodapé devem ser evitadas. Quando imprescindíveis, devem ser numerados consecutivamente e aparecer ao pé da página apropriada.

Agradecimentos (facultativo)

Devem vir após o texto, e antes das referências, tendo como objectivo agradecer a todos os que contribuíram para o estudo mas que não têm peso de autoria. Nesta secção é possível agradecer a todas as fontes de apoio, quer financeiro, quer tecnológico ou de consultadoria, assim como contribuições individuais.

Abreviaturas

Não use abreviaturas ou acrónimos no título e no resumo e limite o seu uso. Abreviaturas não consagradas devem ser definidas na primeira utilização, por extenso, logo seguido pela abreviatura entre parenteses. A menos que a sigla seja uma unidade padrão de medição. Uso excessivo e desnecessário de acrónimos e abreviaturas deve ser evitado.

Unidades de Medida

Devem ser utilizadas as unidades Sistema Internacional de Unidades. As medidas de comprimento, altura, peso e volume devem ser expressas em unidades do sistema métrico (metro, quilograma ou litro) ou seus múltiplos decimais. As temperaturas devem ser dadas em graus Celsius (ºC) e a pressão arterial em milímetros de mercúrio (mm Hg) ou a hemoglobina em g/dL. Todas as medições hematológicas ou bioquímicas serão referidas no sistema métrico de acordo com o Sistema Internacional de Unidades (SI).

Nomes de Medicamentos

Identifique com precisão todos os medicamentos e produtos pelo nome genérico. Não é recomendável a utilização de nomes comerciais de fármacos (marca registrada), mas quando a utilização for imperativa, o nome do produto deverá vir após o nome genérico, entre parênteses, em minúscula, seguido do símbolo que caracteriza marca registada, em sobrescrito (®).

Tabelas e Figuras

Tabelas/Figuras devem ser numerados na ordem em que são citadas no texto e assinaladas em numeração árabe e com identificação, Figura/Tabela.

Cada figura e tabela incluídas no trabalho têm de ser referidas no texto: Uma resposta imunitária anormal pode estar na origem dos sintomas da doença (Fig. 2). Esta associa-se a outras duas lesões (Tabela 1).

Figura: Quando referida no texto é abreviada para Fig., enquanto Tabela não é abreviada. Nas legendas ambas as palavras são escritas por extenso.

Cada tabela e figura deve ser acompanhada da respectiva legenda, sucinta e clara. As legendas devem ser auto-explicativas (sem necessidade de recorrer ao texto).

Em relação aos gráficos deve ser explícito se a informação inclui valores individuais, médias ou medianas, se há representação do desvio padrão e intervalos de confiança e o tamanho da amostra (n).

As fotografias deverão incluir identificadores (setas e asteriscos). Poderão ser publicadas fotografias a cores, desde que consideradas essenciais.

Cada tabela deve ser utilizada para mostrar resultados, apresentando listas de dados individuais ou sumariando os mesmos, não devendo no entanto constituir duplicação dos resultados descritos no texto. Devem ser acompanhadas de um título curto mas claro e elucidativo. As unidades de medida usadas devem ser indicadas (em parêntesis abaixo do nome que encabeça cada categoria de valores) e os números expressos devem ser reduzidos às casas decimais com significado clínico.

Para as notas explicativas nas tabelas devem ser utilizados os seguintes símbolos e sequência: *, †, ‡, §, ||, ¶, **, ††, ‡‡ .

Se fotografias de doentes forem usadas, estes não devem ser identificáveis ou as fotografias devem ser acompanhadas de autorização por escrito para usá-las.

As imagens a cores são reproduzidas gratuitamente.

Princípios gerais:

• Numere as ilustrações de acordo com a sua sequência no texto.

• Forneça as legendas das ilustrações separadamente.

• Dimensione as ilustrações próximas das dimensões desejadas da versão publicada.

• Envie cada ilustração em ficheiro separado.

A inclusão de figuras e/ou tabelas já publicadas, implica a autorização do detentor de *copyright* (autor ou editor).

A submissão deve ser feita separadamente do texto, conforme as instruções da plataforma.

Os ficheiros das figuras devem ser fornecidos em alta resolução, 800 dpi mínimo para gráficos e 300 dpi mínimo para fotografias.

A publicação de ilustrações a cores é gratuita.

Material gráfico deve ser entregue em um dos seguintes formatos:
JPEG (. Jpg)
Portable Document Format (. Pdf)
PowerPoint (.ppt)
TIFF (. Tif)
Excel

Permissão para publicação: No caso de publicação de tabelas de livros ou revistas os autores são responsáveis por obter permissão, junto dos autores dos trabalhos de onde forem reproduzidos, para a referida publicação, e terão de a apresentar na submissão.

Ficheiros Multimedia

Os ficheiros multimedia devem ser enviados em ficheiro separado com o manuscrito. O material multimedia deve seguir os padrões de qualidade de produção para publicação sem a necessidade de qualquer modificação ou edição. Os ficheiros aceitáveis são: formatos MPEG, AVI ou QuickTime.

Anexos/ Apêndices

Quando necessário, os anexos devem ser utilizados para apresentar inquéritos longos ou detalhados, descrições de extensos cálculos matemáticos e / ou listas de itens. Devem ser colocados depois da lista de referências, se necessário, com legendas. Anexos longos, tais como algoritmos, pesquisas e protocolos, serão publicados apenas *online*; o URL será fornecido no artigo impresso onde o anexo é citado.

Se houver mais de um apêndice, eles devem ser identificados como A, B, etc. As fórmulas e equações em apêndices devem ser numeradas separadamente: Eq. (A.1), Eq. (A.2), etc .; Em apêndice posterior, a Eq. (B.1) e assim por diante. Da mesma forma para tabelas e figuras: Tabela A.1; FIG. A.1, etc.

Estilo

Rev Port Endocrinol Diabetes Metab segue AMA Manual Style (10ª edição).

Última revisão **Maio 2017**