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HYPERPROLACTINEMIA AND OTHER ENDOCRINE CAUSES OF INFERTILITY

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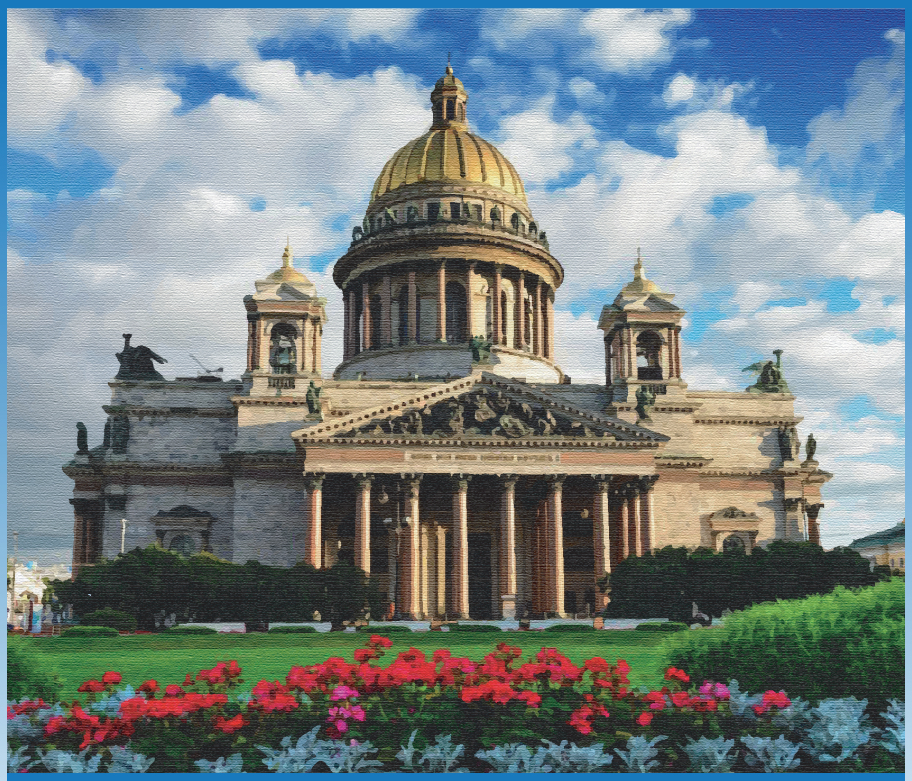
ABSTRACTS



Oral Presentation 01

Abstract-ID: OP01-01
EFFECTS OF THERAPY WITH INOSITOL ALONE OR COMBINED WITH CABERGOLINE ON MENSTRUAL IRREGULARITY AND ANDROGEN LEVELS IN POLYCYSTIC OVARY SINDROME WOMEN WITH HYPERPROLACTINEMIA

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Mild transient hyperprolactinemia affects 30% of women with polycystic ovary syndrome (PCOS). In such patients combined treatment with the dopamine agonist cabergoline (CAB) and the insulin sensitizer metformin reportedly improves menstrual cycles and hormonal profile, whereas no data are available on the effects of combined treatment with CAB and the insulin sensitizer inositol (INO) in PCOS patients. The current study aimed at investigating the effects of combined treatment with CAB+INO on clinical, hormonal and metabolic profile in PCOS patients. Fifty-six PCOS women with PRL 1.3-fold x ULN (>32.5 ng/ml) were randomly assigned to INO monotherapy (Group 1, no=30 patients) or CAB+INO (Group 2, no=26 patients). CAB was added at the dose of 0,25-0,5 mg/week. Clinical [menstrual cycle intervals (MCI), Ferriman-Gallway Score (FGS), weight, BMI, waist circumference (WC)], hormonal [PRL, FSH, LH, estradiol (E2), total testosterone (TT), androstenedione (A)], and metabolic [fasting glucose (FG) and insulin (FI), HOMA-IR, HOMA-beta, total (CHO), HDL and LDL cholesterol, triglycerides (TG) and visceral adiposity index (VAI)] parameters were evaluated before and after 6 months of therapy in the two groups. In both groups age, BMI, hormonal profile and HOMA-IR at baseline were similar. After treatment, PRL levels fully normalized in all patients, with no significant difference between the two groups. In Group 1, INO significantly improved MCI (p=0.005), FGS (p<0.0001) and TT (p=0.021). In Group 2, CAB plus INO significantly improved MCI (p<0.0001), FGS (p=0.001), weight (p=0.003), BMI (p=0.003), WC (p=0.001), E2 (p=0.003), TT (p=0.002), A (p=0.002), FI (p=0.008), HOMA-IR (p=0.005), HOMA-beta (p=0.048), HDL (p=0.05), and LDL (p=0.023). Percent decrease (Δ) in MCI (ΔMCI, p<0.0001), ΔFGS (p<0.0001), Δweight (p=0.001), ΔBMI (p=0.001), ΔWC (p=0.014), ΔTT (p=0.020), ΔA (p=0.014), and ΔFI (p=0.044) were higher in patients treated with CAB+INO as compared to those receiving INO monotherapy. After treatment, one patient in group 1 (3,3%) and 3 patients in group 2 (11.5%) spontaneously conceived. In conclusion, CAB addition to INO might increase therapeutic success in patients with PCOS and hyperprolactinemia by further improving clinical, hormonal and metabolic alterations as compared to INO monotherapy. Further studies are needed to better investigate the potential use of CAB in the therapeutic algorithm of PCOS.

Abstract-ID: OP01-02
SSTR5 IS EXPRESSED IN PROLACTINOMAS AND SUPPRESSES PROLACTIN PROMOTER ACTIVITY

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Prolactinomas are managed with dopamine receptor agonist cabergoline and bromocriptine as the first-line therapy. However, 10-15% of prolactinomas show resistance to dopamine agonists and this prevalence is even higher in macro-prolactinomas that are difficult to get complete curative treatment by surgical methods. Another possible therapeutic option could be treatment with somatostatin analogs, but did not show promise. The development of second generation somatostatin analogs that bind to multiple somatostatin receptors (SSTR) could provide with alternative therapeutic means. The multi-receptor somatostatin analog pasireotide has high affinity for SSTR5 followed by SSTR2, 3 and 1. The aim of the present study was to determine the expression of SSTR2 and SSTR5 on a set of 16 prolactinomas by immunohistochemistry using the specific rabbit monoclonal UMB1 and UMB4 antibodies. Immunoreactivity was scored in a semiquantitative manner from 0 (no signal) to 1 (100% +++). The majority of prolactinomas (13 out of 16) did not show any SSTR2 immunoreactivity. Three out of 16 cases showed SSTR2 immunoreactivity ranging from 0.017 to 0.27; the highest SSTR2 immunoreactivity score (0.27) was observed in a mixed PRL/GH tumor. SSTR5 was detected in the majority (13 out of 16) of prolactinomas with scores ranging from 0.1 to 0.67. We did not find any significant association with patients' age, gender, tumor size, invasiveness, and preoperative serum prolactin levels (SPSSv23). To determine the putative action of SSTR5 on prolactin synthesis we used a rat prolactin promoter luciferase reporter vector. Overexpressing human SSTR5 in the rat mammosomatotrophinoma GH3 cells (that lack endogenous Sstr5) significantly reduced *rPrl* promoter activity (71%±7.6% compared to mock transfected, p=0.0029). SSTR5 overexpression did not significantly affect cell viability as determined by the WST-1 colorimetric assay. Treating SSTR5 overexpressing GH3 cells with pasireotide significantly suppressed *rPrl* promoter activity in a dose dependent manner (IC_{50}=2.65±0.18nM). Altogether our results show that SSTR5 is predominantly expressed in prolactinomas and provide with preliminary evidence for a potential for SSTR5 targeting somatostatin analogs in lowering prolactin synthesis and managing hyperprolactinemia.

Abstract-ID: OP01-03

DIFFERENTIAL GENES EXPRESSION IN HUMAN UMBILICAL VEIN ENDOTHELIAL CELLS IN GESTATIONAL DIABETES CASES: ROLE IN CARDIO-METABOLIC DISEASES PROGRAMMING

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Background: Understanding the mechanism whereby the intrauterine hyperglycemia in women with gestational diabetes mellitus (GDM) affects the offspring' predisposition to metabolic and cardiovascular diseases may help prevent their intergenerational transmission. Our aim was to study the effect of the degree and duration of maternal hyperglycemia on the level of expression of genes associated with cardio-metabolic diseases in human umbilical vein endothelial cells **(**HUVECs) of newborns from women with GDM.

Materials and methods: HUVECs were isolated from 41 women with GDM treated for GDM starting before 30-th week of gestation (GDM1), 9 women treated for GDM after 34-th week of gestation (late treatment group or GDM2) and 17 women without GDM (control group). The level of intercellular adhesion molecules (ICAM1 and VCAM1), angiopoietin-like protein 4 (ANGPTL4), a major glycoprotein of the vascular endothelium - endoglin (ENG), mammalian tribbles homologue 1 (TRIB1), mitochondrially encoded NADH: ubiquinone oxidoreductase core subunit 2 (MT-ND2), mitochondrial transcription factor 1 (TFAM) prostaglandin-endoperoxide synthase 1 (PTGS1), mesoderm specific transcript (MEST), placenta specific 8 (PLAC8) and nuclear receptor subfamily 3 group C member 1 (glucocorticoid receptor) (NR3C1) genes expression was determined by RT-PCR.
Results: Three of the above mentioned genes were associated with GDM: ANGPTL4, MT-ND2 and TRIB1. Both GDM2 and GDM1 groups showed significantly reduced levels of MT-ND2 and ANGPTL4 genes expression as compared to the control group (9.3±5.4, 9.9±23.0 and 56.1±82.8 for MT-ND2 respectively, p=0.007, and 10.4±5.8, 22.3±25.4 and 111.4±129.1 for ANGPTL4 respectively, p=0.014), but no difference was observed between GDM1 and GDM2 groups. TRIB1 gene was differentially expressed among the three groups: 7.5±5.4, 4.9±2.9 and 2.6±0.9 in controls, GDM1 and GDM2, respectively (p=0.003). After comparison in pairs the difference was significant between GDM1 and GDM2 (p=0.0059) and between GDM2 and control group (p=0.0051).
Conclusion: The decrease in MT-ND2, ANGPTL4 and TRIB1 genes expression level has been detected in HUVECs of newborns from women with GDM compared to control group. The duration of hyperglycemia was associated only with TRIB1 gene expression that presumably confirms the role of intrauterine hyperglycemia in cardio-metabolic diseases programming. Further studies are required to prove a cause-effect relationship between ANGPTL4, MT-ND2 genes expression and GDM respectively.
The study was funded by Russian Science Foundation (project №15-14-30012).

Abstract-ID: OP01-04
PRIMARY AUTOIMMUNE HYPOPHYSITIS WITH NORMAL OR ELEVATED PROLACTINEMIA AS CAUSE OF INFERTILITY

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Introduction: As hypopituitarism, secondary hypogonadism occurred from 44 to 100% of patients affected by primary autoimmune hypophysitis (PAH), the aim of this study was to describe causes of sexual disturbances in PAH and to evaluated their outcome according to treatment choice.

Patients and Methods: A retrospective longitudinal monocentric study was conducted on patients with histological or clinical diagnosis of PAH, classified as adenohypophysitis (AH), panhypophysitis (PH) and infundibuloneurohypophysitis (INH) according to clinical and neuroradiological findings

Results: 24 PAH (12 AH, 4 PH and 8 INH) were collected. 8 patients (33.3%) referred sexual disturbances at hypophysitis diagnosis time: 4 patients referred oligo-amenorrhea, 2 patients secondary amenorrhea and 2 patients impotency.
Secondary hypoadrenalism was diagnosed in 9/24 (37.5%), GHD in 5/24 (20.8%), secondary hypothyroidism in 4/24 (16.7%) and secondary hypogonadism in 9/24 (37.5%) patients. Among the 7

female hypogonadic patients, none showed ovulatory cycles. Normal Prolactin value was detected in 12 patients (50%) and low values in 2 patients (8%). Instead, hyper-prolactinemia occurred in 10 patients (41.6%) and coexisted with secondary hypogonadism in 4 patients. In 4 patients, hypogonadism occurred with normal PRL value (p=0.5) and in a single patient with low PRL value. Among hypogonadal group, a single patient was affected also by secondary hypothyroidism and 3 patients also by GHD. Instead among eugonadal patients with sexual disturbances, a single patient was affected by GHD. Secondary hypogonadism occurred more frequently in patients with INH (5/9, 55.6% p=0.04 OR:8; 95%IC:1.1-67.1) as compared to 2 AH cases (22.2%) and 2 PH cases (22.2%). Similarly, GHD was detected only in INH (p=0.002)

All hypogonadal patients underwent immunosuppressive glucocorticoid treatment. During 24-months follow-up, in 6 cases, sexual disturbances recovered (66.7%), according to restore of secondary hypogonadism in all cases, of GHD in 2 patients and of hyper-prolactinemia in 2 patients. Despite immunosuppressive treatment, in 2 patients, secondary hypogonadism persisted, according to the persistence of hypopituitarism and active pituitary inflammation at neuroimaging. At least, a single patient independently after an initial benefit withdrawn glucocorticoid treatment and, at observational follow-up, secondary hypogonadism persisted.

Conclusion: Although rare, hypophysitis, particularly INHs, are important causes of sexual disturbances, for occurrence of secondary hypogonadism, hyperprolactinemia and GHD, in young and potentially desirous of offspring patients. Consequently, if not contraindicated, aetiological treatment with immunosuppressive drug is recommended to improve gonadal status, restoring pituitary function.

Abstract-ID: OP01-05
EVALUATION OF RELATIONSHIP BETWEEN POSTPRANDIAL BLOOD GLUCOSE CURVE AND FOOD INTAKE CHARACTERISTICS IN GESTATIONAL DIABETES PATIENTS

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Background and Aims: Understanding of relationship between postprandial blood glucose (BG) levels and variety of factors influencing blood glucose curve, especially features of preceding food intakes and individual patient characteristics, is important for successful gestational diabetes mellitus (GDM) treatment. The aim of the study was to quantitatively evaluate the relationship between these factors and postprandial glycemic response.

Methods: Week-long glucose levels were continuously monitored in 58 women with GDM by iPro CGMS system. Patients were also given a specially developed app “DiaCompanion”, which they used to keep track on the diet, blood glucose (BG) and physical activity. The records were collected onto a

standardized spreadsheet, sent via E-mail, stored remotely and were afterwards combined with the CGMS data by the use of a specially developed software.

Results: A total of 858 food intakes were analyzed. The features of postprandial curve were: area under curve (AUC), AUC above 7.0 mmol/L, mean value for the period of 1, 2 and 3 hours after the beginning of food intake; BG level after 1, 2, 3 hours; BG peak value after food intake, the time between the beginning of food intake and a peak and the actual rise of BG after food intake. The linear regression model on the basis of food intake characteristics (the amount of carbohydrates, proteins and fats) and patient characteristics (body mass index (BMI), age, pregnancy week) was developed to predict each of these BG curve features. Each of the models had a significant importance of coefficient corresponding to carbohydrates, BMI, age and pregnancy week. As an example, the model predicting peak value on postprandial BG curve had a p-value of $2.37e^{-14}$ for amount of carbohydrates, $2.71e^{-8}$ for age, $3.44e^{-8}$ for pregnancy week, $7.64e^{-7}$ for BMI and only 0.374 and 0.806 for the amount of proteins and fats in a food intake respectively. The prediction power of the model was relatively low, resulting in residual standard error of 0.81 mmol/L and R-squared value of 0.37, which confirms a complex non-linear relation between the features being investigated. The model developed on the same data set, but without patient characteristics resulted in residual standard error of 0.86 mmol/L and R-squared value of 0.29.

Conclusions: The features of postprandial blood glucose curve tend to be highly influenced by individual characteristics of GDM patients, that complicates the development of reliable generalized predictive models for different patients.

The study was funded by Russian Science Foundation (project №15-14-30012).

Abstract-ID: OP01-06

IGF-1 MAY PARADOXICALLY INCREASE WITH CABERGOLINE TREATMENT FOR PROLACTINOMAS

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Objective: Hypersecretion of growth hormone (GH) may be seen in patients harboring prolactin (PRL)-secreting adenomas. Dopamine agonists may decrease levels of IGF-1. However, in adenomas co-secreting GH and PRL, IGF-1 levels often will not normalize. Currently there is no recommendation to monitor IGF-1 levels in patients without clinical phenotype of acromegaly.

Design and Methods: We studied the clinical characteristics and response to treatment of patients with prolactinomas without clinical signs or symptoms of acromegaly, and with normal or mildly elevated baseline IGF-1 levels that paradoxically increased following cabergoline treatment.

Results: The cohort included 10 patients (8 males), mean age at diagnosis 45±15 years. The diagnosis followed investigation of infertility/sexual dysfunction in 9/10 patients. Mean±SD adenoma size was 22.7±17.2 mm, with cavernous sinus invasion in 8 patients. Mean PRL level was 1766±2,880 ng/mL.

Low testosterone was evident in 7 out of 8 males. In 5 patients baseline IGF-1 level was normal and in 4 it was 1.2-1.5-fold higher than the ULN. One had IGF-1 of 1.4xULN measured shortly after cabergoline initiation. Baseline mean GH data, available for 4 patients, was 0.4±0.4 ng/ml. Treatment with cabergoline (0.5-2 mg/week) achieved PRL normalization in all patients and recorded tumor shrinkage in 7 patients. IGF-1 levels increased in all patients, with a mean IGF-1 of 1.8±0.6 x ULN on cabergoline treatment. Cabergoline dose reduction in two patients resulted in decreased IGF-1 levels. IGF-1 also decreased following pituitary surgery in two patients. One patient was given pegvisomant and three were treated with somatostatin analogues, with reduction of IGF-1 levels in all four. After a mean follow-up period of 5.1±2.8 years, 8 patients are still treated with cabergoline, with a current IGF-1 level of 1.1±0.4 x ULN, and five have elevated IGF-1.

Conclusion: In patients harboring prolactinomas, IGF-1 may paradoxically increase to clinically significant levels with cabergoline treatment. As uncontrolled acromegaly may develop in these patients, IGF-1 should be monitored and treated accordingly.

Oral Presentation 02

Abstract-ID: OP02-01
PREDICTIVE FACTORS OF NON-FUNCTIONING PITUITARY ADENOMA IN PATIENTS WITH MILD HYPERPROLACTINEMIA

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Background: Hyperprolactinemia can be caused by not only excessive hormone production from a prolactinoma but also disinhibition of hypothalamic-pituitary dopaminergic pathways due to other pituitary macroadenomas. As standard treatments of prolactinoma and non-functioning pituitary adenoma (NFPA) are different, it is important to discriminate the two types of tumors. The aim of this study is to evaluate clinical and radiological markers for discriminating NFPA with hyperprolactinemia from prolactinoma.

Methods: We reviewed 85 patients with mild hyperprolactinemia (25 ng/mL ≤ serum prolactin < 200 ng/mL) who underwent transsphenoidal adenomectomy (TSA) between January 2012 and December 2013 at the Severance Hospital, Seoul, Korea. We grouped the patients according to the immunohistochemistry results. Biochemical parameters, clinical parameters and radiological findings including tumor size, T2 signal intensity on MRI were evaluated retrospectively.

Results: Patients with NFPA were older than those of prolactinoma (47.5 vs. 32.3 years, p <0.001). They had longer tumor diameter (24.0 vs. 10.1 mm, p <0.001) and lower serum prolactin levels (53.3 vs. 101.3, p <0.001), even though this study include only the patients with mild hyperprolactinemia. Symptoms caused by pituitary mass effect, such as headache or visual field defect, or incidentally diagnosed cases were frequent in patients with NFPA, whereas amenorrhea or galactorrhea were more common in prolactinoma group. Analysis about signal intensity of pituitary adenomas on T2-weighted MRI showed that most of NFPA were hyperintense (97.0%) A multivariable logistic regression analysis demonstrated larger tumor sized and hyperintensity on T2-weighted MRI were associated with NFPA than prolactinoma.

Conclusion: In patients with mild hyperprolactinemic pituitary adenoma, tumor size and T2 signal intensity on MRI can be useful markers for discriminating NFPA from prolactinoma to determine the appropriate treatment method.

Abstract-ID: OP02-02

DOPAMINE RECEPTORS DR-D2 EXPRESSION BY INMUNOHISTOCHEMISTRY IN PATIENTS WITH DIAGNOSIS OF MENINGIOMAS

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Introduction: Meningiomas (MNG´s) are the most common intracranial tumor in adults. Even though surgical resection offers excellent outcomes, there is a subgroup of patients with MNG´s surgically unaffordable, refractories to conventional therapies, invasive, recurrent, atypical or anaplastic. These patients require effective alternative treatments and despite technological advances, currently their options are very limited or null. Through the stimulation of dopamine receptors (DR), dopaminergic agonists (DA) have proved an antiproliferative effect in multiple neoplasias. MNG´s express DR in their cell membrane, nevertheless, the type of DR varies according to the detection technique used.

Results: This study analyzed 23 MNG´s, 10 females (43%) and 13 males (57%), mean age was 44.5 years, who underwent surgical resection between 2010 and 2014 at our institution. The tissue was immunohistochemically evaluated for the presence of Ki-67, Dopamine D1 and Dopamine D2 receptor. Tumors were classified according to the Worlh Health Organization (WHO) as Grade I (70%), Grade II (13%) or Grade III (17%). The mean expression index was Ki-67= 18.9 (Range: 7.0-50.8), DR-D1= 23.02 (range 2.9-65.0) and DR-D2= 8.33 (Range: 0.1-45.8). We used the Stata Data Analysis and Statistical Software Version 11 to analyzed if there was a relationship with any of the variables and between markers. None of the markers showed significant relationship with the expression among them, nor the expression, localization or histopathological features. Ki-67 expression index showed significant relation with the mean age (p= **0.03**) and prolactin levels (p= **0.02**).

Conclusion: MNG´s express DR-D2 detectable with immunohistochemistry. This finding is novel and promising, since the stimulation of the DR-D2 activates an intracellular inhibitory response, and the DA with the ones we have experience treating other tumors bind the D2 receptor. Further studies will help to clarify the real effect that the DA could have in the medical treatment of MNG´s.

Abstract-ID: OP02-03

SERUM KISSPEPTINS LEVEL IN HEALTHY AND HYPOGONADOTROPIC BOYS

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Background. Kisspeptins, ligands of G protein–coupled receptor 54 (GPR54) encoded by the KiSS-1 gene, have recently emerged as key players of the gonadotropic axis.

It was found that KiSS-1/GPR54 system plays an important role in the neuroendocrine control of gonadotropin secretion, brain sex differentiation, puberty onset and fertility. It is important to know if the kisspeptin serum level could be used as a diagnostic criterion to the stage of puberty or impairment of it in boys.

Objective To investigate the possible relation between the serum level of kisspeptin and different stages of puberty in healthy boys and boys with delay of puberty onset due to hypogonadotropic hypogonadism.

Methods. 39 boys in total were examined. They were divided into three groups. Group 1 (control, prepubertal boys aged 4-10 years old, Tanner I, n=15). Group 2 (control, pubertal boys aged 14-17 years old, Tanner IV-V, n=16). Group 3 (hypogonadotropic boys aged 14-17 years old, Tanner I, n=8). Hypogonadotropic hypogonadism in boys was confirmed by the median (Me) of basal level of testosterone (T) 0,33 nmol/l, Me LH 0,3mU/l, a Gn-RH-stimulated LH value less than 5 IU/l. In all the groups the serum level of kisspeptin was examined by immunoassay (Cloud-Clone Corp., USA). The data was expressed as mean values (M+m).

Results. The level of kisspeptin in blood in group 1 and 2 did not have any differences (16,27+2,23 pg/ml and 14,11+1,71 pg/ml respectively, p>0,05). Unlike the above, the level of kisspeptin in group 3 was significantly higher than in both groups 1 and 2 (50,91+14,43 pg/ml as opposed to 16,27+2,23 pg/ml, p<0,01; 50,91+14,43 pg/ml as opposed to 14,11+1,71 pg/ml, p<0,002 respectively).

Conclusions. The serum level of kisspeptins was found to be equal in boys, sexually developed regardless of their age and stage of puberty. In contrast, the level of kisspeptins was significantly higher in boys affected with gonadotropic hypogonadism. It can be caused by GPR54 insensitivity or loss of biological activity of kisspeptin. The latter condition can be corrected by novel therapeutic technologies such as treatment with exogenous kisspeptin.

Abstract-ID: OP02-04

RESISTANT PROLACTINOMA: A COHORT OF 30 ISRAELI PATIENTS

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Introduction

Prolactin secreting tumors are the most common pituitary adenoma type. Prolactinomas cause hormonal disturbances in women and males, and also mass effects if the adenomas are large enough. These tumors usually respond to treatment with dopamine agonists.

Aims and Methods

We have identified 30 patients (22 males) in three medical centers, diagnosed between 1991-2015 with resistant prolactinomas, defined as prolactin levels above 3 times the upper limit of normal (ULN) or adenoma growth despite a weekly dose of ≥2 mg of cabergoline.

Results

Mean age at diagnosis was 31±14 (13-62). 25 of 30 patients had macroadenomas, 4 of them were giant tumors (>40 mm); 4 patients had microadenomas. The adenoma size at presentation was not available for one patient. Twenty five (83%) were invasive and 16 (53%) patients had visual field deficits. Mean baseline prolactin was 273±618 X ULN (range, 2.9-2870). At diagnosis 14 of 22 males presented with hypogonadism, and 6 of 8 females had amenorrhea. Mean maximal weekly cabergoline dose was 5.2±3.9 mg (range, 2-15). With dopamine agonist treatment adenoma size decreased significantly in 18 of 25 subjects with available data for tumor shrinkage. Mean minimal prolactin level on dopamine agonist decreased to 17±33 X ULN (median, 5), and 11 of 16 patients with visual damage improved. Eighteen patients (60%) underwent pituitary surgery (trans-sphenoidal, 16; craniotomy, 2). Eight (26%) patients received radiotherapy following surgery.

Currently, 11 patients (36%) have prolactin levels of 3XULN and below, 6 of them normalized prolactin. Testosterone was normalized in only one male presented with hypogonadism..

Conclusions

Resistant prolactinomas are uncommon, and usually require multi-modal treatment strategy. In our cohort we were able to control 11 of 30 resistant tumors.

Abstract-ID: OP02-05
PROLACTINOMA MANAGEMENT: PREDICTORS OF REMISSION AND RECURRENCE AFTER DOPAMINE AGONISTS WITHDRAWL

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Objective*:* Prolactinomas are the most common functional pituitary tumour. Dopamine agonists (DA) are its principal treatment. The criteria that should guide therapy withdrawal and the factors that influence disease remission or relapse are not yet fully established. Our purpose is to evaluate the proportion of patients who attempted DA withdrawal, and to identify the factors that influence clinicians to try it. In addition, we aim to study the factors that are involved in prolactinoma remission/relapse after therapy withdrawal.

Method*:* We retrospectively evaluated 142 patients with prolactinoma diagnosis who had been treated exclusively with DA. Firstly, the patients were divided in two groups, according to whether DA withdrawal had been attempted, or not, and the factors that might predict clinicians' decision to discontinue the therapy were then analysed. Secondly, patients who attempted withdrawal were further divided into two subgroups, based on their remission or relapse *status* and predictors of remission were evaluated.

Results*:* DA withdrawal was attempted in 35.2% of our patients. Females, subjects with lower initial serum prolactin (PRL) levels, those with microadenomas and those with longer treatment duration all had a higher probability of seeing their therapy discontinued. In the withdrawal group, the remission rate was 72%. Macroprolactinomas relapse more often than microprolactinomas ($p<0.05$). The

recurrence group had higher median initial serum PRL levels and a lower mean duration of therapy, however these variables did not reach statistical significance.

Conclusion*:* We found a low percentage of attempt of withdrawal of DA therapy in the subjects with prolactinoma. Our data confirms that DA therapy can be discontinued with a high remission rate. Tumour size was the main variable that affected the withdrawal outcome in our patients.

Poster Presentation

Abstract-ID: P01-01
SYNDROM HYPERPROLACTINEMIA IN PATIENTS WITH ACROMEGALY

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The purpose: to evaluate clinical data in patients with acromegaly, depending on the level of prolactin.

Material and methods: 50 patients with acromegaly were selected. The average age of the patients was 48.5±11.2 years. Based on the level of growth hormone (GH) and prolactin (PRL), patients were divided into 2 groups: I group - patients with elevated levels of GH - pituitary somatotropinomas-32(64%) patients; (men 14(43.75%) and women 18(56.25%)). Group II - patients with elevated levels of GH and PRL - pituitary mammosomatotropinomas - 18(36%) patients (men 7(38.9%) and women 11(61.1%)). The effectiveness of treatment for clinical manifestations, MRI and hormone levels (GR, IGF-1, PRL) was evaluated.

Results: The analysis of the average hormonal parameters in patients of the two groups was: Igroup GH 94,5±66,4mMe/l, IGF-1 867,8±94,6ng/ml, PRL 12,5±8,2ng/ml; IIgroup 8.3±21.8mMe/l, 667.6±81.6g/ml, 139.7±78.2g/ml respectively. The level of prolactin is higher in patients with pituitary mammosomatotrophinomas than in patients with somatotropinomas, and the level of GH versus.

The most common clinical manifestations in the study groups were the following: coarsening of facial features - in Igroup 24(75%) patients; IIgroup 10(55.6%); an increase in the limbs 23(71.9%), and 11(61.1%); headache 12(37.5%) and 8(44.4%) patients, respectively.

Numbness in the arms and legs was observed in Igroup 20(62.5%); IIgroup 3(16,6%) cases, diabetes mellitus type 2 (34,4%) and 1(5,56%) cases, decreased libido and potency 2(6.25%) and 6(33.3%), respectively. In women - menstrual irregularities in Igroup occurred in 2(11.1%), in IIgroup in 6(54.5%), galactorrhea 1(5.6%) and 4(36.4%) patients. In patients with the Igroup, the clinical picture was characterized by the severity of hypersomatotropinemia, while in the II group, hyperprolactinemic syndrome with lactorrhea-dysmenorrhea appeared against the background of the blurred acromegaloid symptom of the complex.

Conclusions. Hypersomatotropinemia in 36% of cases is combined with an increase in the level of prolactin, which is the result of mammosomatotropic adenoma of the pituitary gland and needs a pathogenetic approach to the selection of medications in their treatment. The level of prolactin is a good differential diagnostic criterion in patients with mammosomatotropic adenomas of the pituitary gland.

Abstract-ID: P01-03
DIFFERENCES IN PROLACTINOMAS PRESENTING IN ADOLESCENCE/PREADOLESCENCE AND IN THE ELDERLY: COMPARATIVE CLINICAL STUDY

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BACKGROUND: Studies focusing on clinical and hormonal characteristics of prolactinomas in the childhood / adolescence and in the elderly are scarce. Even more scarce is data covering the comparison of these two populations.

OBJECTIVE: We aimed to assess clinical characteristics of prolactinomas in patients diagnosed before the age of 25 and after the age of 70, and to compare the two groups.

METHODS: Pituitary adenoma (PA) database of the Department of Neuroendocrinology for the past twelve years was audited and 183 patients were identified with pituitary adenoma diagnosed either prior to age of 25 (n=118) or after the age of 70 (n=65). Eighty-one patients (44.3%) had prolactinoma. Gender, age at diagnosis and tumor size were analyzed in all patients.

RESULTS: We identified 77 patients with prolactinoma (9 males, 68 females) diagnosed prior to 25 years of age and 4 PA patients (all males) diagnosed after the age 70. Prolactinoma was the most common functional PA in young patients (77/118, 65%). Growth hormone secreting adenoma was the most prevalent PA in elderly, followed by prolactinoma (n=4). Female gender was significantly more prevalent in the younger group ($p<0.01$) and male gender in the elderly group ($p<0.01$). Mean age at diagnosis was 21.3 ± 0.3 years (range, 12-25 years) and 71.3 ± 0.6 years (range, 71-72 years), respectively. In the younger group, 20 patients (25%) were younger than 20 years at diagnosis. FIPA was found in 2 young patients and 1 elderly patient with prolactinoma (1.6%) and MEN1 in 2 young patients with prolactinoma. Prevalence of macroprolactinomas was significantly greater ($p<0.01$) in the elderly than in the young. Seventeen young patients (22%) had macroprolactinomas (mainly occurring in girls, n=11), 5 (6.5%) had mezoprolactinoma, and 55 (71.5%) had microprolactinomas. Contrary to this, in the elderly group, all 4 patients had macroprolactinomas.

C**ONCLUSION:** Clinical characteristics of patients diagnosed with prolactinomas in adolescence and in the elderly age group were significantly different. Female gender and microprolactinoma was significantly more prevalent in the younger group, while male gender and macroprolactinoma in the elderly group.

Abstract-ID: P01-04
TO THE QUESTION OF DIAGNOSTICS OF HYPERPROLACTINEMIC SYNDROME IN REAL CLINICAL PRACTICE

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Purpose: to study the correctness of the diagnostics of hyperprolactinemic syndrome in real practice.

Methods: a retrospective analysis of 92 patient case histories (12 men, 80 women) with a diagnosis of hyperprolactinemic syndrome was conducted. The following parameters were analyzed: the presence of indications to the definition of prolactin, whether there was a question about taking medications that increase the concentration of prolactin, and whether the patient was provided with information on the rules for compliance with the preanalatic stage.

Results: Among 90 patients in 78 (10 men, 68 women) there were no indications to the definition of prolactin, namely: menstrual disorders, infertility, decreased libido, galactorrhea. Most often the definition of prolactin was due to the "study of the hormonal background" in the list of most hormones. Of these 90 patients, 80 (12 men, 68 women) repeated prolactin level were normal, so the previous results were regarded as false positive, and the diagnosis of hyperprolactinemic syndrome was withdrawn. Of all 90 patients, only 7 were provided with information on the rules of the preanalytical stage. The information about taking medications that increase the concentration of prolactin was presented only in 3 case histories. The were performed brain MRI among 5 patients on the basis of a single increased level of prolactin /without compliance with the rules of the preanalytical stage and exclusion of drugs which cause hyperprolactinemia/. When a negative result was obtained, two of them were recommended to repeat brain MRI with contrast agents. Of the 10 patients diagnosed with prolactinoma (pituitary microadenoma), nine were assigned cabergoline, while one patient was recommended surgical removal as an initial treatment.

Conclusion: in the vast majority of cases, the determination of the concentration of prolactin in the blood is prescribed without any indication. There is no differential diagnosis with other causes of hyperprolactinaemia; Patients do not stipulate the conditions for the analysis to exclude false positive results. Since single definition of prolactin is reccomended according to clinical guidelines of Endocrine Society, compliance with the rules of diagnosis is extremely relevant.

Abstract-ID: P01-05
NEUROLOGICAL MANIFESTATIONS AS INITIAL PRESENTATION OF INVASIVE AND GIANT PROLACTINOMAS

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Objective: To describe atypical neurological presentations of invasive and giant prolactinomas and report their response to dopamine agonist (DA's) therapy.

Methods:

A case note analysis of all patients with diagnosis of invasive and giant prolactinomas attending to neuroendocrine clinic between 1998 and 2015. Those with atypical neurological manifestations at diagnosis were examined in detail.

Results: presentations were documented in 33 out of 180 patients who harbored invasive or giant prolactinomas (15%), 73% males, median age at diagnosis: 29 years (IQR 12.5) with median basal prolactin level: 7,972 ng/mL (1,125-20,000, IQR 12, 484); 82% had giant tumors. The frequency of the different presentations was: seizures 36%, hydrocephalus 18%, ophtalmoplegia 12%, pituitary apoplexy 15%, cerebrospinal fluid (CSF) leakage 9%, psychiatric disorder 4%, hemiplegia 4%, lower cranial nerves palsies 4%, nasal obstruction 4%. Treatment with cabergoline in 27/33 (82%) or bromocriptine in 6/27 (18%) resulted in improvement of clinical data from presentation and a reduction of prolactin levels, at one month 87% in men and 75% in women, with a reduction of 95% upon last follow up. Median tumor size reduction with treatment was 69% (30-100%) after a median follow up of 4.6 years.

Conclusions: Giant and invasive prolactinomas have neurological presentations and commonly are confused with other diseases, leading to a delay in diagnosis. Primary treatment with dopamine agonists effectively reduces prolactin levels as tumor size, up to recover the neurological manifestations of the disease.

Abstract-ID: P01-06
PROLACTINOMAS IN SERBIAN FIPA PATIENTS

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For the past eight years, in the Department of Neuroendocrinology, we have identified 33 families and 70 family members diagnosed with familial isolated pituitary adenomas (FIPA). Among these there were twenty families, in whom at least one member was diagnosed with prolactinoma (families

with only prolactinomas (n=6), families with different adenoma types PRL/NF (n=6), PRL/ACRO/GIGANT (n=6), PRL/NF/ACRO (n=1) and PRL/CUSH (n=1). Among total of 27 FIPA patients with prolactinomas, majority were females (20/27) with microadenomas (24/27). Macroprolactinomas were found in only 3 patients (1 male and 2 females). All patients with macroprolactinomas came from families affected by gigantism and acromegaly. In addition to this, two patients with acro/gigantism had mixed GH/PRL macroadenomas. However the AIP mutation (R304E) was detected in only one young female patient , who was diagnosed with macroprolactinoma at the age of 15. In general, as expected, female patients were diagnosed with prolactinoma at considerably younger age compared to males (26.3±3.2 years vs 39.6±6.3 years, $p<0.05$).

In conclusion, prolactinomas are considerably prevalent among FIPA families in Serbia. At least one member is affected by prolactinoma in 60% of FIPA families. Prolactinomas account for 38.6% of all pituitary adenomas in our FIPA patients, followed by somatotropinomas and nonfunctioning adenomas in 30% of patients. respectively. Although majority are microadenomas in female patients, special attention and genetic testing is recommended in young patients with macroprolactinomas.

Abstract-ID: P01-07
GIANT PROLACTINOMA COMPLICATED BY CEREBROSPINAL FLUID RHINORRHOEA FOLLOWING DOPAMINE AGONIST THERAPY

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Giant prolactinomas defined as pituitary PRL-secreting adenomas whose size exceeds 40 mm are very rare. Their treatment and outcome can be unpredictable and challenging for clinicians. We present a patient with enormous prolactinoma-size 70 mm complicated by cerebrospinal fluid (CSF) rhinorrhoea following bromocriptine therapy.

Case report: Forty-seven years old male was referred to our department by a neurosurgeon due to hormonal evaluation because his cranial MRI had showed a large intra-, para- , retro-, antero- and suprasellar pituitary tumor. He had suffering from intensive headache and visual deterioration the last year, with sexual dysfunction. For the last three years he had received more than 15kg of body weight. Hormonal evaluation detected extremely high serum PRL levels of 706210 mU/l and incomplete hypopituitarism. His testosterone and thyroxin levels were decreased, cotisol in low normal range while IGF1 concentration was adequate for age. Visual field was reduced in terms of bitemporal hemianopsia. Bromocriptine therapy was included, the dose was gradually increased until to 15 mg daily. He has tolerated the drug well but two months after the start of this therapy, CSF leaks was appeared in the patient. He underwent neurosurgery where tumor was partially resected with transnasal endosocpic repair of CSF rinorrhoea. Histopathology revealed PRL secreting tumor. Patient has continued with bromocriptine at the same dose. Close follow-up every 3-6 months years has detected a rapid decrease in PRL level and tumor shrinking (MRI) with visual field improvement and body weight reduction. For 4 years of cabergoline treatment complete biochemical and clinical remission has been achieved in our patient. We have noticed a recovery of his pituitary function.

Conclusion: giant prolactinomas are invasive adenomas but well responsive to dopamine agonists. However, CSF rhinorrhoea can occur at any time on treatment with dopamine agonist suggesting a need for vigilance throughout therapy.

Abstract-ID: P01-08
PROLACTINOMA AND EPILEPTIC SEIZURES

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Objective: to study epileptic seizures in patients with prolactinomas.

Patients and Methods: 68 patients with prolactinoma: 45 patients – large prolactinoma is more 36 mm in diameter and 23 patients – giant prolactinoma is more than 60 mm in diameter. 55 men and 13 women (16-67 years, mean 39).

Patients were followed by hormone measurements, magnetic resonance imaging (MRI), electroencephalogram (EEG) and endocrinological, psychopathological, neurologic examinations.

Mean serum prolactin level ranged between 12990 and 1038000 mU/l (mean 198000 mU/l). Diagnosis of epileptic seizures was based on the detection of typical pathological patterns in EEG.

Results: Epileptic syndrome was revealed in 14 patients (21%): partial seizures with secondary generalization (64%), complex (28%) and simple (14%) seizures or their combinations.

Seizures differed in structure depending on growth of the tumor. Partial seizures with secondary generalization were mostly revealed in patients with growth of adenoma to temporal region on left (50%) and right (14%). Complex partial seizures were revealed in patients with growth of the adenoma to temporal region on left (21%) and into the III ventricle (7%). Simple partial (psychosensory) seizures were in patients with growth of adenoma into diencephalon region (14%).

Conclusion: Patients with prolactinomas have epileptic seizures. The structure of epileptic seizures depends on the diameter of the adenoma and a certain direction of growth with the effect on other areas and structures of the brain.

Abstract-ID: P01-09
GONADOTROPE-TESTICULAR AXIS IMPAIRMENT (GTAI) IN MEN WITH PROLACTINOMA AND IN THOSE WITH NON PROLACTIN-SECRETING HYPOTHALAMIC-PITUITARY LESIONS: A SINGLE-CENTER COMPARATIVE STUDY.

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Context and Aim. GTAI is observed in patients with prolactinoma. GTAI is caused by either hypothalamic kisspeptin/GnRH deficiency and/or by pituitary mass effects directly affecting gonadotrope function. The aim of this study was to compare the degree of GTAI in men with prolactinoma with that caused by non-prolactinoma hypothalamic pituitary lesions (np-HPL).

Patients and Methods. This study has been conducted at a tertiary referral center. We included 102 men with prolactinoma (microadenoma, n=12 and macroadenoma, n=90) and 380 with np-HPL: non-functioning pituitary adenoma (n=146); acromegaly (n=92); Cushing disease (n=18); intracranial tumors (n=56); infiltrative (n=24) apoplexy (n=16), iatrogenic, traumatic or idiopathic (n=29). Testicular volumes (TV), LH, FSH, total (TT) and bioavailable (BT) testosterone, estradiol, SHBG, inhibin B, AMH and insulin-like factor 3 (INSL3) were determined.

Results. Age at diagnosis and BMI were not different between men with prolactinoma and those with np-HPL. Similarly, mean TV were not different between men with prolactinoma (17.4±7.8 mL) and those with np-HPL (15.6±6.3 mL, p=0.15). Mean TT was higher in prolactinoma than in np-HPL patients (1.83±0.89 versus 1.45±0.99 ng/mL, p=0.001). Similarly, mean BT levels were higher in men with prolactinoma than in np-HPL (0.71±0.39 versus 0.58±0.44 ng/mL, p=0.008). No significant differences in LH, FSH, inhibin B, AMH or INSL3, estradiol or SHBG serum levels were found in subjects with prolactinoma and in those with np-HPL. Compared to men with prolactinoma, those with np-HPL had more frequently been subjected to neurosurgery (49.9% versus 17.8%, p<0.0001) or radiotherapy (16.3% versus 1%, p<0.0001). Fewer patients with prolactinoma had corticotrope insufficiency than those with np-HPL (15.6% versus 39.5%, p<0.0001).

Conclusions. GTAI seems milder in men with prolactinoma than in those with np-HPL. The higher TT and BT levels might most likely depend on the lower rate of demolitive surgery or radiotherapy, as well as the lower rate of corticotrope deficiency in prolactinoma than in np-HPL patients.

Abstract-ID: P01-10
PROLACTINOMAS IN SERBIAN FIPA PATIENTS

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Over the past eight years, we have identified 33 families and 70 family members diagnosed with familial isolated pituitary adenomas (FIPA) in the Department of Neuroendocrinology, Belgrade. Among these there were twenty families, in whom at least one member was diagnosed with prolactinoma (families with only prolactinomas (n=6), families with different adenoma types PRL/NFPA (n=6), PRL/ACRO/GIANT (n=6), PRL/NFPA/ACRO (n=1) and PRL/CUSH (n=1)). Of the 27 FIPA patients with prolactinomas, majority were females (20/27) with microadenomas (24/27). Macroprolactinomas were found in 1 male and 2 females. All patients with macroprolactinomas came from families affected by gigantism and acromegaly. In addition, two patients with acromegalic gigantism had mixed GH/PRL macroadenomas. However, the *AIP* variant *(R304Q)* was detected in only one young female patient, who was diagnosed with macroprolactinoma at the age of 15. In general, as expected, female patients were diagnosed with prolactinoma at considerably younger age compared to males (26.3±3.2 years vs. 39.6±6.3 years, p<0.05).

In conclusion, prolactinomas are prevalent among FIPA families in Serbia. At least one member is affected by prolactinoma in 60% of FIPA families. Prolactinomas account for 38.6% of all pituitary adenomas in our FIPA cohort, followed by somatotropinomas and nonfunctioning adenomas in 30% of patients. Although the majority are microadenomas in female patients, special attention and genetic testing is recommended in young patients with macroprolactinomas.

Abstract-ID: P01-11
COMPARSION OF PATIENTS WITH DOPAMINE AGONISTS SENSITIVE AND RESISTANT PATIENTS PROLACTINOMAS

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Aim: To compare clinical, laboratory, and instrumental characteristics of patients with dopamine agonist sensitive (DAS) and resistant (DAR) prolactinomas.

Materials and methods: The study included 101 patients: 44 pts with dopamine agonist sensitive (29 women and 25 men) and 57pts with dopamine agonist resistant (41 women, 16 Men) prolactinomas. Criteria of resistance: the lack of normalization of prolactin (PRL) level and/or absence of adenoma shrinkage by 50% or more during 6+ months of cabergoline intake of >3 mg/week.

Results: DAR patients were younger than DAS, 31 [26; 38] versus 37 [29; 49] years, p = 0.014. At the time of diagnosis, DAR patients were also younger than DAS, 20 [15; 30] versus 31 [23; 46] years, p <0.001. The duration of the disease in DAR patients was much longer than in DAS, 8 [3; 13] versus 3 [1; 8] years, p <0.001. Clinical manifestations in general did not differ in sensitive and resistant patients. In women, menstrual irregularities at the onset of the disease were common in all patients, but among DAR women with prolactinomas, primary amenorrhea was more likely to be diagnosed (39% vs. 7%, p = 0.043). When analyzing laboratory data, PRL at the onset of the disease was higher in DAR patients 5033 [3514; 17547] mU/l vs. 3623 [2332; 12720] mU/l, p = 0.035. The tumor volume in the debut of the disease did not differ among these two patient groups. In both groups, there was a correlation between the level of PRL and tumor volume (Spearman correlation coefficient for sensitive r = 0.56, p <0.001, for resistant - r = 0.55, p <0.001). During treatment with cabergoline DAR prolactinama patients this correlation persist (R = 0.38, p = 0.011), whereas in DAS the normalization of PRL was rapid, tumor volume reduction occurred more gradually, and this correlation was lost (r = -0.23, p = 0.155). Invasive and suprasellar growth of adenomas were significantly much more frequent in DAR patients (67% versus 37%, p <0.001 and 49% vs. 12%, p <0.001, respectively). Bitemporal hemianopsia was diagnosed in 21% of DAR patients with prolactinomas and non cases in DAS (p = 0.001).

Conclusions: In DAR patients, the disease was diagnosed on average 10 years earlier and persisted longer. They have higher levels of PRL at the time of diagnosis. Their pituitary tumors more often show invasive and suprasellar growth.

Abstract-ID: P01-12
PROLACTINPOOL VS. SINGLE SAMPLE DETERMINATION

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Introduction: The assessment of pituitary function is often achieved by means of sequential determinations (pool) of hormone levels such as prolactin and gonadotrophins. For the determination of prolactin levels the guidelines of the Endocrine Society are clear in recommending a single sample determination. **Objective:** To evaluate differences between single sample and pool (0', 20' and 60') determinations for assessing prolactin. **Methods:** We conducted a cross-sectional study including 4610 prolactin pools. Statistical analysis was performed using the paired samples *t* test. **Results:** We found differences between prolactin levels in determinations at 0', 20' and 60' (21.5±64.6 vs 19.7±63.7 vs 18.8±63.8 ng/mL, p<0.001) and also between the prolactin level at 0' and the mean of the three determinations (21.5±64.6 vs 20.0±63.9 ng/mL, p<0.001). The mean difference between prolactin levels at 0' and 20' was 1.8±7.6 ng/mL, at 0' and 60' 2.8±8.6 ng/ml and at 20' and 60' 1,0±7.1 ng/mL. **Conclusion:** Despite the presence of differences in hormone levels between pool determinations these differences, given its range, do not appear to have clinical significance.

Abstract-ID: P01-13
CLINICAL AND BIOCHEMICAL FEATURES OF HYPERPROLACTINEMIC WOMEN FORM MOSCOW REGION

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The goal: to assess the clinical and hormonal features of prolactinomas in female patients from Moscow region.

Material and Methods: Clinical and hormonal data of 136 patients with hyperprolactinemia were analyzed: MIcroadenomas (n=52, 38%), MAcroadenomas (n=42, 31%), NonTumor hyperprolactinemia (n=42, 31%). MRI was performed on high field instrument Intera Achieva (PHILIPS company) 3.0 TL, with intravenous extracellular gadolinium contrast agents. All hormonal determinations were performed by an enzyme-linked Immunosorbent assay. The results were analyzed using statistic methods for nonparametric data and expressed as Me [25%; 75%].

Results: Age distribution was 36.5 (25; 46), 50 (34; 61) and 37 (27; 44) y.o., respectively (NS). Prolactin levels were in MI 1500 (1052; 2278), MA 3095 (1729; 18784) and NT 1574 (1154; 2185) mE/l, accordingly (p=0.002). There was positive correlation between prolactin levels and tumor volume (r=0.45, p<0.001). Menstrual cycle was regular in 48% of MI and 50% of NT; 45 % of MA were postmenopausal. Menstrual disturbances were opsomenorrhea (MI 36%, MA 18%) and amenorrhea (MI 16%, MA 24%, NT 17%), prolactin levels were higher in symptomatic MI compared with asymptomatic (p=0.012), and were similar in pre- and postmenopausal subgroups (p>0.05). Galactorrhea was observed in 29% of MI, 19% of MA and 21% of NT (including cases of galactorrhea without menstrual disorders). Headache and visual disturbances were observed in 45% and 14% of MI, 86% and 48% of MA, 50% and 10% of NT, respectively. First patients' complaints were: in MI – menstrual disorders (65.7%), galactorrhea (22.9%), headache (14.3%), infertility (8.6%), visual disorders (2.3%), other complaints (8.6%); in MA – headache (36.6%), visual disorders (29.6%),

menstrual disorders (29.6%), other complaints (14.1%). The most often “first referred” specialists were: in MI – gynecologist (84.8% of patients of reproductive age), neurologist (6.1%), ophthalmologist (3%), endocrinologist (9.1%); in MA – gynecologist (42.3% of patients of reproductive age), neurologist (31%), ophthalmologist (19.7%), therapist (5.6%), endocrinologist (2.8%), other specialists (8.5%).

Conclusions: Patients with pituitary microadenomas were younger than patient of pituitary macroadenomas. Approximately half of patients with microadenomas and nontumoral hyperprolactinemia were asymptomatic with prolactin levels < 3000 mE/l. For symptomatic patients main clinical signs were menstrual disorders and/or galactorrhea in microadenomas and nontumoral hyperprolactinemia, headache and visual disturbances in macroadenomas.

Abstract-ID: P01-14
MIGHT SERUM PROLACTIN LEVELS PREDICT TUMOR SHRINKAGE IN PITUITARY ADENOMAS ASSOCIATED WITH ISOLATED HYPERPROLACTINEMIA?

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Background Prolactin-secreting pituitary adenomas (PRLomas) represent the most frequent pathological condition associated to hyperprolactinemia (hyperPRL). However, patients harboring a nonfunctioning pituitary adenoma (NFPA), particularly those with a macroadenoma, may present a mild-moderate hyperprolactinemia due to pituitary stalk compression or stretching. In this context, dopamine agonists (DAs) represent the treatment of choice to reduce/normalize serum PRL levels. Moreover, while DA treatment results in tumor size reduction in the majority of PRLomas, this is not the case for NFPAs. Therefore, the main aim of our study was to evaluate retrospectively the biochemical and tumor response to treatment with DAs in a large number of pituitary adenomas associated with isolated hyperPRL, trying to identify a cut-off value of baseline PRL levels able to predict tumor shrinkage.
Patients and Methods Out of 204 pituitary adenomas with isolated hyperPRL referred to our Center, 117 (77 F; mean age 38.5 yrs; 53 macroadenomas) had a clear description of the DA treatment schedule, as well as of tumor volume changes in their clinical records and were included in the study. Pituitary function and adenoma size were evaluated at baseline and at the end of DA treatment (mean follow-up 6.2 yrs).
Results Baseline PRL values were 946 ± 2294 µg/L (mean ± SD) and were significantly reduced at the end of DA treatment (29 ± 77 µg/L, p<0.0001). Most patients (108/117, 92%) were treated with cabergoline (mean dose 1.2 ± 0.7 mg/week). 71 out of 117 adenomas (61%) showed tumor shrinkage, as indicated by the reports of dedicated neuroradiologists. Adenomas with tumor volume reduction had significantly higher baseline PRL levels compared with those with stable/increased tumor mass (mean PRL 168 vs. 115 µg/L; p=0.031). Considering only macrodenomas, this difference was even more evident (PRL 706 vs. 254 µg/L; p=0.007). In this light, ROC analysis (including both micro and macroadenomas) showed a 63% sensitivity and 66% specificity for a PRL cut-off value of 144 µg/L. For macrodenomas only, PRL values >377.5 µg/L resulted in 66% sensitivity and 70% specificity. Post-treatment PRL values, correlated with tumor volume reduction, and suppressed serum PRL levels (<2 µg/L) were mostly found in patients showing tumor shrinkage (p=0.01).

Conclusions DA treatment was effective in the control of hyperPRL and resulted in tumor shrinkage in about 60% of adenomas. Basal PRL values were higher in patients showing tumor reduction, likely indicating the presence of a PRLoma. However, the possible presence of DA resistant PRLomas and

NFPAs responsive to medical treatment makes difficult the identification of PRL cut-offs able to predict tumor shrinkage with higher sensibility and specificity in this subset of pituitary adenomas.

Abstract-ID: P01-15
LESS PARTICIPATION AND AUTONOMY IN PATIENTS WITH A PROLACTINOMA ARE ASSOCIATED WITH MORE IMPAIRMENTS IN QUALITY OF LIFE

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Objective: After biomedical treatment, patients with a prolactinoma report impairments in quality of life (QoL). In recent qualitative focus group conversations these patients reported persistent issues such as, fatigue, concentration/attention problems, melancholy, mood swings, and a changed personality. As a consequence they experienced difficulties in picking up their 'normal' life and they reported problems related to performing their work. The aim of the present study was to quantitatively assess participation and autonomy in patients with a prolactinoma and to examine whether impairments in participation and autonomy are associated with QoL.

Design: Cross-sectional evaluation of 88 patients with a prolactinoma. In order to measure participation and autonomy the Impact on Participation and Autonomy questionnaire (IPA) was used. This measure assesses several aspects including autonomy indoors, family role, autonomy outdoors, social life and relationships, and work and education. QoL was assessed with the Short-form 36 (SF-36) and the Hospital Anxiety and Depression Scale (HADS). Reference data were derived from recent studies and included patients with multiple sclerosis with severe fatigue (n=263), rheumatoid arthritis (n=395) or chronic obstructive pulmonary disease (n=326).

Results: Patients with a prolactinoma reported better participation and autonomy on four of the five domains of the IPA (i.e., autonomy indoor, family role, autonomy outdoors, social life and relationships) compared to the reference groups ($P \leq .001$). On the other hand they reported worse participation and autonomy on the domain 'work and education' compared to all reference groups ($P < .05$). Furthermore, less participation and autonomy (all domains) were associated with worse physical functioning ($r \geq -.503$, $P \leq .001$), worse social functioning ($r \geq -.498$, $P \leq .001$), more physical role limitations ($r \geq -.383$, $P \leq .001$), more emotional role limitations ($r \geq -.280$, $P \leq .001$), more pain ($r \geq -.387$, $P \leq .001$) (SF-36), more anxiety ($r \geq .355$, $P \leq .001$), and more depressive symptoms ($r \geq .375$, $P \leq .001$) (HADS).

Conclusion: Patients with a prolactinoma reported more impairments in participating in work and education compared to reference groups. Furthermore, less participation and autonomy were related to more impairments in QoL. These findings need to be taken into account in the follow-up of these patients. Furthermore, these findings can be used for optimizing care trajectories and/or the development of a specific rehabilitation program for patients with a prolactinoma.

Abstract-ID: P01-16
VISUAL FIELDS EVALUATION AND PROLACTIN LEVELS ACCORDING TO TUMORAL SIZE OF INVASIVE, GIANT, AND MEGA GIANT MACROPROLACTINOMAS

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Objectives: to describe visual improvement in response to dopaminergic agonists (DA) treatment in accordance to tumoral size and prolactin levels in patients who received treatment for macroprolactinomas.

Material and methods: We divided 3 groups of treatment according to tumoral size: group 1: less than 4 cms, group 2: 4 to 6 cms and group 3: greater than 6 cms. All three groups with prolactin levels greater than 1,000 ng/mL. Visual fields and prolactin levels were evaluated at first month, one year, 2 years and 5 years.

Results: Retrospective study from 1998 to 2015, where 174 patients received treatment (DA) 51 women, 123 men, prolactin levels: women 6,004.95 ng/mL (1001-22,110), men 7,644.57 (1060-20,300).

Pretreatment evaluation: Group 1: 78 patients: 5,071.33 ng/mL (1,001-19,000). 60/78 (78%) visual disturbances were identified, 18 without visual disturbances. Group 2: 79 patients: 7,552.09 ng/mL (1112-22110), 61/79 (78.4%) with visual disturbances, 18 without visual disturbances, group 3: 17 patients: 10,627.5 ng/mL (4.000-19,357), 15/17 (90.9%) with visual disturbances, only two patients without it. (p=0.002).

A month: Group 1**:** 822.6 ng/mL (1.6-6,476.3), 8/78 improved, 68 were without changes, 2 patients got worse. Group 2: 2,080.81 ng/mL (1.8-13,327.6), 2/79 improved, 70 without changes and 7 presented visual deterioration. Group 3: 3,123.98 ng/mL (8-10,931) no one improved, 15 without changes and 2 got worse.

A year: Group 1: 340.08 ng/mL (0.36-4,014) 11/78 improved, 64 without changes and 3 got worse. Group 2: 682.20 ng/mL (0.6-5,408), 5/79 improved vision, 65 without changes and 9 got worse. Group 3: 3,752.70 ng/mL (0.3-18,885) 3/17 improved, 12 without changes and two got worse.

At 2 years: Group 1: 256.38 ng/mL (1-3,684) 8/78 improved, 58 without changes and 12 got worse. Group 2: 555.99 ng/mL (2-4278), 5/79 improved, 64 without changes and 10 got worse. Group 3 3,296 ng/mL (2-18,121) 2/17 improved, 11 without changes and 4 got worse.

At 5 years: Group 1: 1302.64 ng/mL (1.28-4,568.61) Group 2: 695.45 ng/mL (4.20-6,824) Group 3: 3,413.27 ng/mL (2.4-20,878.51)

Conclusions: Patients with megagiant prolactinomas (group 3) presents visual disturbances in greater percentage than smaller tumors, and don´t improve in spite of proper treatment, in comparison to group 1 and 2 who show greater probability to improve their visual fields. Likewise, group 3 present higher prolactin levels through the time of the study, with lower decrease in values compared to patients with smaller tumors.

Abstract-ID: P01-17

CLINICAL AND MORPHOLOGICAL FINDINGS IN 7 CASES OF PROLACTINOMAS. TRANSCRIPTION FACTORS.

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Transcription factors regulate the development and differentiation of anterior pituitary cells during embryogenesis. The information on the role of transcription factors (TF) is rather controversial.

Materials and methods: we investigated 7 cases of pituitary adenomas in patients with hyperprolactinemia (4 males; 3 females) aged 26 to 68 years and 3 normal adenohypophysis (NAH) obtained from patients (50-69 years) died from cardiovascular diseases. Immunohistochemistry using antibodies against 6 hormones of the adenohypophysis, Ki-67, TFs (NeuroD1, Pit1, Pitx1) was carried out.

Results: Immunohistochemistry has shown that in 2 cases adenomas expressed only prolactin (PRL; prolactinomas), two adenomas expressed PRL and growth hormone (GH; mammosomatotroph adenomas), 2 adenomas expressed PRL and adrenocorticotropic hormone (ACTH; plurihormonal adenomas), one adenoma expressed ACTH (corticotroph adenoma). The patients with acromegaly had GH- and PRL-secreting adenomas. The expression level of Ki-67 was low, it varied from 0,3% to 4,66%, on the average it was 1,49%±1,2%.

The levels of NeuroD1 expression were 98% and 99% in the prolactinomas, 98% and 99% in the plurihormonal adenomas, 98% and 99% in the mammosomatotroph adenomas, 94% in the corticotroph adenoma and in the NAH they were 45%, 60%, 85%. The expression of NeuroD1 in the NAH was +/++, in the adenomas it was +++. The level of NeuroD1 expression in the adenomas was significantly higher than in the NAH (p=0,022).

The levels of Pit1 expression were 0,2% and 1,9% in the prolactinomas, 12,3% and 12,9% in the plurihormonal adenomas, 11,4% and 12,1% in the mammosomatotroph adenomas, 22,7% in the corticotroph adenoma and 83,8%, 98,3% and 98,8% in the NAH. The level of Pit1 expression in the adenomas was significantly lower than in the NAH (p=0,022).

The levels of Pitx1expression were 68% and 96% in the prolactinomas, 32% and 95% in the plurihormonal adenomas, 97% and 98% in the mammosomatotroph adenomas, 86% in the corticotroph adenoma and 16%, 25% and 30% in the NAH. The level of Pitx1expression in the adenomas was significantly higher than in the NAH (p=0,022).

Conclusion: Immunohistochemical studies are essential for confirmation the clinical diagnosis of adenoma hormonal activity. The findings on the expression of pituitary TFs in adenomas and the NAH have corroborated their role in the pituitary adenoma pathogenesis and need further investigations.

Abstract-ID: P01-18
OLFACTORY MARKER PROTEIN MODULATES PROLACTIN SECRETION IN LACTOTROPH

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Objective : Prolactin (PRL) is a hormone that is mainly secreted by lactotrope of the anterior pituitary gland, and is involved in many biological processes including lactation and reproduction. Olfactory marker protein (OMP), a highly expressed a phylogenetically conserved cytoplasmic protein of unknown function found almost exclusively in mature olfactory sensory neurons. Until now, there has been insufficient knowledge on the molecular mechanism of PRL disorders and OMP. In this study, we focused on the molecular relationship between PRL secretion and OMP.

Method : In *vitro* : siRNA Transfection, PRL ELISA assay, Real-time PCR, Western blot

In *vivo*: C57BL/6 genetic background OMP-/- mice were used, Immunohistofluorescence, Tissue culture, PRL ELISA, Western blot

Result : By using RT-PCR and Western blot assay we found that OMP expresses in GH3, GH4 cell lines. In the rat pituitary tissue OMP was co-localized with 90% of PRL secreting cells. Real-time PCR results showed that knock down of OMP in GH4 cells increased PRL mRNA expression compared to the control. More than 2 fold of PRL secretion was observed in siOMP transfected GH4 cells compared to the control. Western blot data showed that knockdown of OMP increased ERK phosphorylation in GH4 cells. Moreover, to investigate the phenotypic response to OMP disruption in pituitary, we used OMP knock-out mice (OMPKO). At the 30 weeks of age, OMPKO serum PRL level was elevated compared to control mice. OMPKO mice exhibited elevated ERK phosphorylation than the OMPWT mice.

Conclusion : In conclusion, the current study indicates that OMP likely to mediate prolactin secretion by modulating ERK phosphorylation in pituitary lactotrope.

Abstract-ID: P01-19
MR-CHARACTERISTICS AS PREDICTORS OF PROLACTINOMA'S HORMONAL AND PROLIFERAL ACTIVITI

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Introduction.
The relationship between T-weighted MRsignals of pituitary adenomas and their growth direction has been recently shown. In somatotropinomas hyperintensive T2-weighted signal was associated with bigger tumor volume compared with hypointensive one.
The goal of this retrospective study was to analyze the MR-characteristics between the T1- and T2-weighted signal intensity of prolactinomas in newly diagnosed patients.
Material and Methods. Pre-treatment T1- and T2-weighted MR-images (Intera Achieva, PHILIPS, 3.0T) of patients from Moscow Regional Registry of pituitary adenomas: 37 microprolactinomas, 80 macroprolactinomas were analyzed, taking into account prolactin levels as well as their dimensions and growth direction. Statistical analysis of the results was carried out using the IBM statistical program SPSS Statistics 20 for Windows 7.0 with variation statistics methods for nonparametric data. The results were expressed as Me [25%; 75%].
Results. The majority of microprolactinomas (75%) had hypointensive T1-signal in the most common combinations with hypointensive T2-signal (50%). In macroprolactinomas group, 44.8% of patients had hypointensive T1-signal in the most common combinations with hyperintensive T2 (20.7%). Median tumour volume in hypoT1 was significantly less in comparison with other types of intensive signal (186.83 [50.76; 1818] mm3 and 2451.5 [269.09; 10281.75], respectively (p=0.003). Pituitary tumour volume and PRL level in the group patients with hypoT1/hyperT2 were 1732 [496,83; 2959,81] mm3 and 16513 [2187; 41957] mMU/l, respectively.

Also median tumour volume in hypoT2 was significantly smaller compared to other types of intensive signal (70.65 [50.24; 1080] mm3 and 1732 [246.59; 8628], p=0.017). There was a tendency that median tumour volume in isoT1/hyperT2 was the highest however the difference was not statistically significant, probably due to low number of cases.
PRL level in the all subgroups of patients did not differ statistically (p>0,05).
Conclusion.
In prolactinomas hypointensive MR-signal (either T1 or T2) was associated with smaller tumor volume. HypoT1 / hypoT2 was detected with a predominant frequency in microprolactinomas. So further investigations should be carried on to prove the diagnostic value of these results.

Abstract-ID: P01-20
ENDOSCOPIC TRANSSPHENOIDAL SURGERY OF MICROPROLACTINOMAS: A REAPPRAISAL OF CURE RATE BASED ON RADIOLOGICAL CRITERIA

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Background: Current standard treatment of microprolactinomas (MIP) is dopamine agonist therapy. As this drug treatment is lifelong in up to 80% of cases, many patients consult pituitary surgeons regarding a surgical alternative. To identify prognostic criteria for surgical remission, we reviewed our series of MIP treated with endoscopic transsphenoidal surgery for patient outcome, with special emphasis on MR adenoma delineation and position.

Methods: Our study cohort comprises a single center series of 60 patients operated for histopathologically verified MRI unequivocally identifiable endosellar microprolactinoma between 2003 and 2016. In 32 patients the adenoma was enclosed by pituitary gland (Group ENC), in 28 patients the adenoma was located lateral to the gland with close relationship to the medial cavernous sinus wall (Group LAT).

Results: After a mean follow-up of 28 months (range 4 to 120 months), remission rate was significantly higher in pituitary adenomas enclosed by pituitary gland (Group ENC) than if they were located lateral to the gland (Group LAT), with 88% vs. 54%, P = 0.004. Intraoperatively, 4 patients showed signs of invasiveness into the medial cavernous sinus wall. Preoperative Prolactin levels did not differ between the groups (mean 191 ng/ml vs. 184 ng/ml in group ENC and LAT, respectively). Severe complications (postoperative cerebrospinal fluid leak, diabetes insipidus, meningitis, ophthalmoplegia) occurred in 1.3% in Group LAT.

A binary logistic regression model revealed that only the radiological criteria applied showed a significant correlation (P = 0.04) with endocrine remission.

Conclusion: According to our results, remission rate is significantly higher in MIPs enclosed by the pituitary gland. However, the decision for surgery should take into account surgeons experience and possibility of complications.

Abstract-ID: P01-21

PRIMARY MEDICAL TREATMENT OF HYPOGONADISM IN MEN WITH TUMORAL HYPERPROLACTINEMIA

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BACKGROUND:
Prolactinomas are the most common type of benign hormone-secreting pituitary tumors. In men with prolactinomas the most common symptoms are related to hypogonadism, including decreased libido and erectile dysfunction. Most, but not all, men with sexual dysfunction and hyperprolactinemia have low testosterone levels.
OBJECTIVE: The objective of this study was to characterize of andrological status in adult males with tumoral hyperprolactinemia (microprolactinomas) and investigating the effects cabergoline (CAB) treatment on the status.
METHODS: We prospectively investigated in 25 men with microprolactinoma (age 22–51 yr). The hormonal profile examined was prolactin (PRL), FSH, LH, TSH, total testosterone (TT), SHBG, estradiol. Measurement of free T (FT) calculated (cFT) according to Vermuelen formula (at http://www.issam.ch/freetesto.htm). Patients were divided into 3 groups: group A of 7 men with microprolactinomas presenting with TT levels within the normal range (>12 nmol/l), group B 8 microprolactinoma men with borderline baseline TT (8-12 nmol/l) and group C 10 microprolactinoma patients with low TT levels (<8 nmol/l).
RESULTS:
Mean TT levels at presentation were 16,1 ± 0,78 nmol/l in group A (range, 12,8.-21,4 nmol/l), 8,76 ± 0,21 nmol/l in group B and 6,1 ± 0,7 in group C ($p < 0.001$). Mean serum prolactin level before treatment was 1012,3 ± 73,5 µIU / ml in group A (range 671-1123,03 µIU / ml.), 1329,2 ± 71,7 µIU / ml in group B, 1318,4 ± 80,1 µIU / ml in group C Following treatment, PRL levels normalized in 92% (23/25) patients. Symptoms of hypogonadism were present in 49%, 54% and 82% of men in groups A, B and C, respectively. After 12 months of therapy with cabergoline, TT level increased from 16,1 to 24,7 nmol/l (Δ = 8,51 nmol/l) in group A, from 8,76 to 14,6 ng/ml (Δ = 5.84 nmol/l) in group B, and from 6.1 to 8.7 nmol/l (Δ = 2.6 nmol/l) in group C ($p < 0.001$ for each group). Symptoms of hypogonadism improved following CAB treatment in 89% of symptomatic men in group A, 55% men in group B, 57% men in group C.
CONCLUSIONS:
In the case of clinical manifestations of hypogonadism in its comprehensive diagnosis, it is mandatory to evaluate the level of prolactin, since normal testosterone does not exclude the probability of prolactinoma in men. When use CAB treatment, testosterone levels in these men can increase higher within the normal range together with improvement in clinical symptoms.

Abstract-ID: P01-22
EFFICIENCY OF CABERGOLIN (A DOPAMIN-RECEPTOR AGONIST) IN TREATMENT OF WOMEN WITH TUMORAL HYPERPROLACTINEMIA

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BACKGROUND:
Hyperprolactinemia is one of the frequent causes of menstrual dysfunction and the associated infertility. Efficiency of drug treatment in patients with tumoral hyperprolactinemia (microprolactinomas) is effective has been fluctuated in a wide range from 52.6% to 85%.
OBJECTIVE: The aim of this study is formulated in its title. We examined the efficiency of individualized dose cabergoline (a dopamine-receptor agonist) in treatment women with tumoral hyperprolactinemia (microprolactinomas).
METHODS: The study population included 30 women. The average age is 33.2 + 6.8 [21-46] years. Inclusion criteria were the age of 19-45, tumoral hyperprolactinemia (microprolactinomas). Exclusion criteria were patients with empty sella syndrome, macroprolactinemia phenomenon, the presence of a mental disorder requiring long-term antipsychotic medication, the use of other drugs that promote hyperprolactinemia, pregnancy and postpartum lactation, hypothyroidism, renal, hepatic failure. The patients included 5 bromocriptine-resistant, 2 bromocriptine-intolerant, and 23 previously untreated women.
RESULTS: Violation of the menstrual cycle was observed in 87% (26/30). Often there were oligo - and opsomenorea (67%, 20/30), amenorrhea (7%, 2/30), polymenorrhoea (3%, 1/30) and dysmenorrhea (10%, 3/30). Galactorrhea occurred in 13% of patients (4/30 people). The asymptomatic course of hyperprolactinemia of tumor origin was noted in 4 women out of 30 cases (13%). Violation of sexual function (we used SFQ questionnaire) was noted in 14 patients out of 30 (47%).
We increased cabergoline dose on the basis of individual prolactin levels. Length of treatment was 1 year. Cabergoline normalized hyperprolactinemia in all patients
Before treatment the mean prolactin level was 989.5 ± 497 (957.2; 540-2406) µIU / ml. During treatment the mean prolactin level was 235 µIU / ml [127-419] ($p<0,001$). Cabergoline normalized hyperprolactinemia and recovered the ovulatory cycle in 26 patients. Oligo-and opsonenorea was preserved only in 4 patients out of 30, amenorrhea, polymenorrhoea, dysmenorrhea was not noted in any patient. Violation of sexual function (according to the SFQ questionnaire) was preserved in 1 patient (3%).
CONCLUSIONS:
1. The most common clinical symptom in women with tumoral hyperprolactinemia (microprolactinomas) was violation of the menstrual cycle (87%), in some women decreased libido and galactorrhea (47% and 13%, respectively).
2. Individualized cabergoline treatment can normalize hyperprolactinemia in nearly all microprolactinomas irrespective of tumor size or preceding treatments.

Abstract-ID: P01-23
EFFICACY OF CABERGOLINE A SELECTIVE DOPAMINE MIMETIC IN TREATMENT OF PATIENTS WITH HYPERPROLACTINEMIA

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Due to selective dopamine mimetics in XXI century hyperprolactinemia can be corrected.

Aim: to assess efficacy of selective D2 receptors agonists (cabergoline) in patients with hyperprolactinemia syndrome (HPS).

Materials and methods: we examined 65 patients with HPS, 43 women and 22 men among them aged from 17 to 74years (means age 45.5years).

Prolactin, TSH, STH and, if necessary estradiol, LH, FSH were assayed by EIA and RIA ("ImmunoTech" commercially available kits, Czech Republic) in all patients. MRI was used to visualize chiasmatic-sellar region. If necessary, ultrasonography was used to examine the genitals and liver, neuro-ophthalmological and neuroimaging were performed.

All patients were divided into two groups by size of the tumor. 39 patients with microprolactinomas was included into the 1st group, 26patients with macroprolactinomas with prolactin varying from 132 to 211ng/ml comprised the 2nd one.

Cabergoline was prescribed in the dose of 1 -3mg a week by the size of the tumor and prolactin levels. Efficacy of treatment was assessed within 3-6 months.

Results: Microprolactinomas were in 30 women and 9 men with mean prolactin level 134±11.7ng/ml and adenoma volume 336 mm (0,3%) Mean prolactin levels in 13 women and 13 men included into the 2nd group were 146±12.5ng/ml and pituitary adenoma volume 616 mm (0,16%).

In 3 months prolactin levels in the 1st and 2nd groups were 32.1ng/ml and 45.7ng/ml, respectively. MRI showed adenoma size reduction by 29.7% and 16.2% in the 1st and 2nd group, respectively.

In 6 months prolactin levels in the 1st and 2nd groups were 14.0ng/ml and 32.0ng/ml, respectively. In the 1st group prolactin could be seen restored to normal values in 34 patients (2.9%), in 5 cases (20%) prolactin level remain increased. In the 2nd group prolactin restoration could be seen in 20(5%) patients, in 6(16.7%) prolactin levels resisted to correction. Significant reduction was not observed, and macroprolactinomas were recommended to be surgically removed due to potential risk to the chiasm and blindness.

In 6 months in the 1st group neither normalization of prolactin levels nor reduction in the adenoma volume could be seen in 2 patients (50%); surgical removal of microprolactinomas was recommended. In the 2nd group the similar picture could be seen in 3 patients (33.3%); surgical removal of macroprolactinomas was recommended.

Conclusion: D2 receptor agonists are believed to be highly efficient in treatment pituitary prolactinomas and to facilitate normalization of clinical-hormonal parameters in patients with microprolactinomas (n=5, 20%) and in patients with macroprolactinomas (n=3, 33.3%). In 18 patients of 65(5.6%), sensitivity to cabergoline was relatively low aggravated by high risk for sight damage.

Abstract-ID: P01-24

VISCERAL FAT, LIPIDS AND ADIPONECTIN IN FEMALE PATIENTS WHO NORMALIZED PROLACTIN (PRL) ON LONG TERM DOPAMINE AGONIST (DA) TREATMENT

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Introduction: Hyperprolactinemia is associated with carbohydrate and lipid metabolism abnormalities. Beneficial metabolic changes were seen after treatment with DA. Whether long term normalization of prolactin with DA lead to full normalization of body composition, lipids and circulating adiponectin it is not known.

Aim: to compare body composition, body mass index (BMI), lipids, circualiting level of adiponectin and indicators of visceral obesity between female prolactinoma patients with long term normoprolactinemia on DA and controls.

Material and methods: 28 non obese female prolactinoma patients and 16 healthy controls (32.63±6.51 vs 36.31±6.94 years old) were recruited. Patients were on Bromocriptine or Cabergoline from 2.0 to 19.0 years. Morning level of PRL, FT4, FT3, TSH, FSH, LH, estradiol, IGF I, total cholesterol (TC) triglycerides, HDL-C, LDL-C, non HDL –C, adiponectin were measured. BMI, waist circumference, lipid accumulation product (LAP), waist hip ratio (WHR), visceral adiposity index (VAI) were calculated. Body composition was measured in 18 patients and all controls by using bioelectric impedance analyzer.

Results: PRL was normalized (10.91±3.65 vs. 9.8 vs 3.69 ng/ml). Other anterior pituitary functions were normal. Levels of TC, triglycerides, HDL-C,LDL-C, non HDL-C were in reference range and similar in both groups. There were no differences in body fat and body composition. Waist circumeference and WHR were in normal range, but significantly higher in patients group (81.6051±1,74 vs 71.87±5.50 cm, p=0.005; 0.828±0,04 vs 0.77±0.06, p=0.003). LAP was normal in both groups (20.31±17.85 vs 11.434, p=0.07). VAI was similar between groups. Adiponectin was normal in both groups. Linear correlation analysis confirmed only significant positive correlation between PRL and adiponectin (r=0.534; p <0.001). Multiple regression analysis showed only PRL was independent predictor of adiponectin level (t=4.08; p< 0.001).

Conclusion: These results suggest that prolactinoma patients with long term normoprolactinemia on long term DA therapy have not higher lipids and visceral fat as cardiovascular risk markers than general population. In these patients secretion of adiponectin is preserved. Normal PRL value is independent predictor of adiponectin secretion which is consistent with literature data.

Abstract-ID: P01-25

PRIMARY CABERGOLINE TREATMENT OF GIANT PROLACTINOMAS.

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OBJECTIVE: prospective study of cabergoline effect in newly diagnosed patients with giant invasive prolactinomas.
PATIENTS AND METHODS: The study group included 121 patients with giant prolactinomas (tumors larger than 40 mm in size); among them 49 patients had tumors larger than 60 mm in size. 91 male and 30 female aged 16-67 years (median 37) were treated with 0.5- 3,5 mg/week (mean 1,5 mg) cabergoline. The treatment period was 6 - 120 months (median 18).
RESULTS: Before treatment 117 (97%) patients had hypogonadism, 99 (82%) - visual impairments, 71 (59%) - headaches, 29 (24%) - epileptic syndrome.

Serum prolactin level before treatment ranged between 12990 and 2210000 mU/l (median 198000; normal 30-545 mU/l). Decrease of prolactin occurred in 114 (94%) patients; prolactin level was normalized during treatment in 49% of cases; 98/121 (81%) patients had significant adenoma shrinkage; 77/99 (78%) patients with pre-treatment visual abnormalities had visual improvement, 67/71 (95%) - headache regression.
In 17 patients cerebrospinal fluid (CSF) leakage occurred within 3-6 weeks, in 1 case - in 76 months after initiation of treatment. In 15 patients endoscopic endonasal surgery for fistula repair was performed; in 2 patients the CSF leakage ceased after diuretic therapy and temporarily cabergoline dosage decrease; 7 (6%) patients had rapid progression cabergoline-resistant tumors. They had surgery followed by stereotactic radiotherapy. PRL-secreting pituitary carcinomas with intra- and extracranial metastases were diagnosed in 3 cases; 5 (4%) patients showed tumor enlargement due to intratumoral hemorrhage.
CONCLUSION: Cabergoline should be the first-line therapy for giant invasive prolactinomas. Use of cabergoline results in effective reduction of prolactin, improvement of visual defects and provides tumor shrinkage. However, patients with giant prolactinomas are at a risk of CSF leakage and tumor enlargement during primary cabergoline treatment.

Abstract-ID: P01-26

HORMONAL AND METABOLIC EFFECTS OF LONG-TERM CABERGOLINE WITHDRAWAL IN PATIENTS WITH HYPERPROLACTINEMIA

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Hyperprolactinemia is associated with abnormalities in glucose and lipid profile with development of insulin resistance and metabolic syndrome (MetS), which have been found to be improved by treatment with cabergoline (CAB). The current study aimed at investigating hormonal and metabolic effects of long-term CAB withdrawal in patients with prolactinomas. In 46 patients (37 F, 9 M, aged 34.5±11.5 yrs, 36 microadenomas and 10 macroadenomas) anthropometric [weight, BMI, waist circumference (WC)] and metabolic [fasting glucose (FG) and insulin (FI), total (TCHO), HDL and LDL cholesterol, triglycerides (TG), HOMA-IR, HOMA-β, ISI0, VAI, and prevalence of MetS] parameters, and PRL levels were evaluated at baseline, at CAB withdrawal (TWD), and 12 (T12) and 60 (T60) months after CAB discontinuation. CAB treatment (median duration= 72 months) induced PRL normalization in all patients, and a significant improvement of BMI ($p<0.0001$), WC ($p<0.0001$), FI ($p=0.007$), HDL ($p<0.001$), LDL ($p<0.001$), HOMA-IR ($p=0.012$) and ISI0 ($p=0.05$) compared to baseline. CAB withdrawal resulted in prolonged and sustained normoprolactinemia, with only 8 (17.4%) patients requiring treatment restarting within 12 months. In 38 patients permanently discontinuing CAB, compared to TWD BMI ($p<0.0001$), WC ($p<0.0001$), TCHO ($p<0.001$) and VAI ($p<0.0001$) significantly impaired at T12, and similarly BMI ($p<0.0001$), WC ($p<0.0001$), TCHO ($p<0.05$) and VAI ($p<0.0001$) at T60. Compared to TWD no further changes were seen in FI, HOMA-IR, HOMA-β, ISI0. MetS prevalence significantly increases from T0 (23.9%) to T60 (41.3%, $p<0.0001$), with 8 patients (17.4%) developing MetS after CAB withdrawal. In conclusion, CAB discontinuation significantly worsens lipid profile and MetS prevalence in patients with prolactinomas.

Abstract-ID: P01-27

PROLACTINOMAS: CLINICOPATHOLOGICAL PREDICTIVE FACTORS FOR EFFICACY OF TRANSSPHENOIDAL SURGERY.

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Background: The treatment of choice in Prolactinomas are dopamine agonists, with surgery reserved for cases refractory to or poorly tolerant of pharmacotherapy. Little is known on the relationships between clinical and histopathological features and their influence on transsphenoidal surgery efficacy. **Objective:** To evaluate clinicopathological aspects of surgically treated PRL-secreting pituitary adenomas, with a particular emphasis on factors affecting treatment efficacy. **Methods:** This cohort study included 48 patients (44 females) aged 30.1±9.2 years, qualified for surgery due to unsuccessful medical treatment. Clinical, hormonal, imaging parameters, and surgical outcomes were evaluated. **Results:** The group included 26 microadenomas (54.2%) and 22 macroadenomas (45.8%). 88.6% of females presented with secondary, and 11.4% with primary, amenorrhea. Headaches had been reported by 37.5% and visual disturbances by 6.3% of patients. The mean duration of symptoms prior to surgery was 5.4±3.7 years. The mean maximum tumor diameter was 12.2±6.6 mm (range: 3–38 mm). The median pre-operative PRL level was 232.5 mcg/dL (IQR: 151.8–407.8). There was a significant correlation between PRL levels and both the maximum tumor diameter and patient age: (r_s=0.629, P<0.001 and r_s=0.361, P=0.012, respectively). The median PRL level was 3.4 mcg/dL (IQR: 1.2–13.7) on postop. day 1 and 10.7 mcg/dL (IQR: 4.1–18.8) at month 3. PRL levels were within reference range in 79.2% on 1st day and at month 3, respectively. Mean follow-up was 82.2±34.6 months), with a 70.8% remission rate at the end of follow-up. The rates of secondary hypothyroidism and hypoadrenalism were low at 4.2% and 2.1%, respectively, with no cases of permanent diabetes insipidus. Remission rates were higher in the case of microadenomas than macroadenomas (84.6% vs. 54.4%; P=0.022). Low tumor invasiveness (Knosp 0–1) was associated with a higher remission rate (84.2%) compared to grade 2–4 tumors (20%; P<0.001). None of the patients with Knosp grade 3–4 tumors (n=6) were cured. Plurihormonal adenomas (mostly alpha-subunit immunopositivity) were detected in 8 patients (16.7%). Plurihormonality was associated with lower remission rates at month 3 compared to pure lactotroph tumors (50% vs. 88.6%, respectively; P=0.011). Ki-67 expression was ≥3% in 25.6% of cases. There was no association between Ki-67 expression and tumor diameter or remission rate (P=0.263 and P=0.957, respectively). A logistic regression model showed that the remission rate at month 3 depended mainly on tumor invasiveness (Knosp 2-4) rather than the maximum diameter (P<0.001 and P=0.185, respectively). **Conclusion:** Surgical removal of prolactinomas is an effective and safe treatment method, with efficacy depending more on tumor invasiveness (Knosp grades 2-4) than on other parameters, such as tumor size, plurihormonality, or proliferation marker expression.

Abstract-ID: P01-28

ANALYSIS OF INDICATIONS FOR SURGICAL TREATMENT IN PATIENTS WITH PROLACTINOMAS

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Purpose: Drug treatment is fist line method in patients with prolactinomas. Only a small number of patients require surgery. Aim: To study the indications for surgical treatment in patients with prolactinomas according to medical data.

Materials and methods: Retrospectively the medical data of 25 patients (10 men, 15 women aged 23-67 years) with prolactinomas who underwent the transsphenoidal endoscopic surgery(TSS) were analyzed. Pituitary MRI results, drug therapy history, indications for surgery were analyzed.

Results: According to pituitary MRI - 17 (68%) patients harbored macroadenoma, 7 (28%) giant adenoma (>4cm), and 1 (4%) microadenoma. The indication for surgery in a patient with microadenoma was the resistance to dopamine agonists and pregnancy desire. Among patients with giant adenomas (5(71%) women 2(29%)-men), the indication to TSS in all cases was resistance to cabergoline, optic chiasm compression and in one case the compression of the VII and VIII cranial nerves. Five (20%) patients were re-operated due to the continued growth of pituitary adenoma after the previous surgery. Dopamine agonist's therapy was applied in 21 (84%). The indications to TSS in these patients were: the resistance to treatment in 5 patients, resistance to dopamine agonists and optic chiasm compression in 14 patients, pituitary adenoma apoplexy in one case and one patient refused long-term drug therapy. In no one case the dopamine agonist dose was not equal or exceeded 2mg/week. Four (16%) patients with macroprolactinomas were operated due to the signs and symptoms of optic chiasma compression without attempts of drug therapy.

Conclusion: The main indications to TSS of prolactinomas were the dopamine agonist's resistance and optic chiasm compression syndrome. But a more aggressive use of dopamine agonists could lead to a reduction in the number of operated patients.

Abstract-ID: P02-01
THE CORRELATION BETWEEN SERUM PROLACTIN AND GROWTH HORMONE POSTNATALLY.

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BACKGROUND: In the neonatal period, ptuitary hormones including prolactin (PRL) and growth hormone (hGH) are secreted in high amounts due to immature feedback mechanisms. As both PRL and hGH are secreted in part by the same somatomammotrophic cells, we investigated their relationship in neonates in relation to sex, gestational week, method of delivery and anthropometric data.

METHODS: Serum levels of PRL and hGH were measured in blood from 225 newborns. Newborn data were extracted from medical records.

RESULTS: A positive correlation was found between log-transformations of PRL and hGH ($r=0.17$; $p=0.01$; $n=225$), with a stronger correlation in newborns whose blood samples were taken more than 2 days after birth ($r=0.42$; $p<0.001$; $n=130$). Log-transformations of the PRL/hGH ratio demonstrated a positive correlation with the gestational week ($r=0.39$; $p<0.001$; $n=200$). Multiple regression

analysis showed that 15% of the variance in the logarithm of this ratio is attributed to the gestational week.

CONCLUSION: In newborns, serum PRL and hGH levels show a positive correlation that can be explained by common regulatory factors or a drift phenomenon. A higher gestational week is associated with a higher PRL/hGH ratio. Further studies are planned to determine whether this PRL-hGH relationship exist in other states such as acromegaly and prolactinoma.

Abstract-ID: P02-02
MOLECULAR MARKERS AND RECURRENCE RISK IN CRANIOPHARYNGIOMA

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Craniopharyngiomas (CP) are rare tumors that are still shrouded by several areas of uncertainty. In some isolated studies, the presence of functional estrogen receptors (ER) has been reported in these neoplasms. These receptors, as well as other molecules such as β-catenin, E-cadherin and Ki67 might be related to the overall risk of recurrence.

Material and methods: Descriptive retrospective observational study. We included all patients with confirmed histology of CP and tissue sample available admitted to the Endocrinology Department from Virgen Del Rocio University Hospital (Seville, Spain) from January 2000 to December 2013. ER, β-catenin, E-cadherin and Ki67 specific stains were done following standard procedures, quantifying the intensity of the stain and correlating the results with tumor recurrence. Quantitative variables are expressed as Median [Interquartile Range], while qualitative ones are expressed as number of patients/patients with available data (percentage)

Results: The total sample includes 29 patients (12 male and 17 female). Overall age at diagnosis was 28,5 years[7,25-46,00]. By age group, 12 were children (Up to 18 years old) and 17 were adults. In those patients with positive ER, we observed an increased rate of recurrence: 12/16 (75,0%) versus 2/8 (25,0%) in case of negative ER stain (p=0,019). Also, we found higher recurrence rates when Ki67 staining per high power field was >10%: 2/3 (66,7%) in comparison with Ki67<10% (None of them showed recurrence, p=0,033). We did not identify significant differences regarding β-catenin or E-cadherin.

Conclusions: In our series, CP presenting with positive ER, as well as Ki67 stain >10% per high power field are more likely to develop recurrence than their negative/<10% counterparts.

Abstract-ID: P02-03

HYPERPROLAKTINEMIA AS ANINDICATOR OF THE PITUITARY ADENOMA GROWTH

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Objective: To find a connection between the sizes of the pituitary adenoma and the level of prolactin.

Material and methods. Extent of the study: there were 80 patients with various pituitary adenomas, including women - 52 (65%) and men - 28 (35%).

The mean age of patients varied 52.5 ± 3.7.By their functional activity adenomas divided as follows:

- GH-secreting pituitary adenomas (acromegaly) 34 (42.5%);

-Hormonally inactive adenomas of pituitary 38 (47.5%);

- ACTH-dependent Cushing's syndrome 6 (10%);

Patients with prolactinomas were excluded from the study due to the high levels of prolactin. Patients of this group, regardless of the size of the adenoma, were examined by the RIA method (Strantg 300, Czech Republic).

All patients were subject to a full standard examination, depending on the type of adenomas. They had the following tests performed: determination of the levels of GH, IGF1 1, ACTH, cortisol, prolactin, TSH, MRI of the pituitary gland, neuro-ophthalmological examination.

Results. For the achievement of the mentioned purpose the patients were divided into 3 groups:

1. Patients with microadenomas, including those causing ACTH-dependent Cushing's syndrome 4 (5%), GH-secreting 3 (3.75%), inactive adenomas 4 (5%).

2. Patients with macroadenomas (50) including those causing ACTH-dependent Cushing's syndrome 2 (2.5%), GH-secreting 29 (36.25%), Inactive adenomas 19 (26.25%).

3. Patients with giant adenomas with an all-out type of growth: GH-secreting pituitary adenomas 3 (3.75%), inactive pituitary adenomas 15 (18.75%).

The results of the levels of prolactin in these 3 groups of patients varied as follows: In the group 1, the prolactin level comprised 22.5±1.7 g/ml, in the group 2 - 47.4±2.1 ng/ml and in the group 3 - 65.8±3.2 ng/ml. As can be seen from the results of a comparative analysis, the prolactin level increase in correspondence with the increase of the size of the chiasmo-sellar region, which occurs due to partial or complete compression of the pituitary stalk.

Conclusion: The increased levels of prolactin in the case of non-prolactin secreting pituitary masses can serve as a sensitive criterion for the size of adenoma and dynamics of growth

Abstract-ID: P02-04

HYPERPROLACTINEMIA AS A MANIFESTATION OF HORMONALLY INACTIVE PITUITARY ADENOMA

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Aim. The work was initiated to study prolactin levels in hormonally inactive pituitary adenoma by the size of the tumor.

Material and methods. We examined 85 patients with hormonally inactive pituitary adenomas, 45 women and 40 men among them aged from 18 to 50 years (mean age 44.5±3.85 years). The disease duration from the onset to diagnosis based on the medical history and MRI ranged from 1 to 15 years.

Results and discussion. Guided by the aim of study we divided the patients into three groups. 26 patients with the tumor size up to 10 mm were included into the first group. 33 patients with the tumor size up to 20 mm comprised the second group. 26 patients with the tumor size 30 and more mm were included into the third group. Analysis of hormonal parameters demonstrated correlation between prolactin level and the tumor size. Hyperprolactinemia was registered in 2%, 45% and 100% of patients in the first group, second and third groups, respectively. In patients with macroadenomas hyperprolactinemia was clinically presented in combination with hypopituitarism. Among patients of the third group, chiasmal and cephalgic syndromes, the latter with the oculomotor nerve damage, were the main symptoms; lactorrhea-amenorrhea syndrome came the third.

Conclusions. Quite frequent sign of hormonally inactive adenoma, hyperprolactinemia upon formations in chiasmal-sellar area not always can be an outcome of prolactin-secreting adenomas; the fact is to be taken into account in choosing the treatment tactics.

Abstract-ID: P02-05

PECULIARITIES OF HYPERPROLACTINEMIA IN ADOLESCENTS

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Hyperprolactinemia is mainly the female pathology, its incidence in children and adolescents varies and assessed as 5%. Due to the above, study on HPS clinical peculiarities is of special interest.

Aim: to study clinical peculiarities of hyperprolactinemia in adolescents.

Materials and methods: we examined 53 adolescents aged from 16 to 18 years, 12 males (22.6%) and 41 (77.4%) females among them.

Prolactin, TSH, STH and, if necessary estradiol, LH, FSH were assayed by EIA and RIA ("ImmunoTech" commercially available kits, Czech Republic) in all patients. MRI was used to visualize chiasmatic-sellar region. Ultrasonography was used to examine the genitals; if necessary, neuro-ophthalmological examination was performed.

Results and discussion: among boys, eunochoid bode proportions were observed in 5 (20%), gynecomastia was registered in 8 (12.5%), testicular hypoplasia was found in 2 (50%); sexual development retardation could be seen in 4 (25%), obesity was found in 3 (33.3%). Among girls, late menarche was registered in 17 (5.77%), irregular menses were found in 16 (6.25%), hyperpolymenorrhea could be seen in 7 (14.28%), physical development was retarded in 12 (8.33%). Ovarian hyperandrogeny, hirsutism manifesting in *akne vulgaris* and *seborrhea adiposa* took place in 11 (9%). One girl had congenital hypertensive headache with range of sight disorder, left-sided ptosis and eyeball limitation outwards, and signs of secondary hypercorticoidism.

Among boys, the above examinations helped find craniocerebral injury with hypertensive cephalgia in 3 (33.3%), hypothyroidism with underlying iodine deficiency in 2 (50%), pubertal-juvenile dispituitarism in 5 (20%) and obesity with hepatic steatosis and chronic active hepatitis in 2 (50%) as the causes of the syndrome.

Among girls, one girl was successfully operated for macroprolactinoma with manifestations of panhypopituitarism to be corrected by replacement of thyroid, sex and adrenal hormones at the

moment. Hypothyroidism with underling autoimmune thyroiditis and diffuse goiter took place in 27 (3.7%), ovarian hyperandrogeny syndrome with polycystic and multifollicular ovaries was registered in 10 (10%), CNS tonsil-induced intoxication could be seen in 3 (33%).

Conclusion: hyperprolactinemia in adolescents is a peculiar and functionally reversible disorder progressing due to damage to peripheral endocrine glands and prolactin secretion dysregulation. Adolescents with HPS do not require special correction with dopamine agonists.

Abstract-ID: P02-06
INCIDENCE OF HYPERPROLACTINEMIA WITH CRANIOPHARINGIOMA IN ADULTS BEFORE AND AFTER SURGERY

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Craniopharyngiomas (CF) - a benign tumor of the embryologic origin. The surgical method of treatment is the basic.
OBJECTIVE: to estimate incidence of hyperprolactinemia before and after surgical treatment of CF at different topographical variations, and after transection of the pituitary stalk.
METHODS: The research involved 40 patients older than 18 years (25 women and 15 men) with a mean age - 41 [21; 69] with a verified diagnosis of CF. All patients were operated , in 18 cases the pituitary stalk was transected.
Before and 6 months after the surgery all patients were examined by means of hormonal blood tests (including prolactin). By localizing tumor patients were divided into 3 groups: 1 – at location of the pituitary stalk (15), 2 – combined «the pituitary stalk» and ventricular (10), 3–intraventricular (15).
RESULTS: In group 1: hyperprolactinemia before surgery - 9 (60%) patients, median of prolactin (PRL) - 724 µIU/mL [90-3640]; after surgery - 4 (26 %) patients, median of PRL - 311 µIU/mL [21-1527].
In group 2: hyperprolactinemia before surgery - 3 (30%), median of PRL - 369 µIU/mL [125-4080]; after surgery - 4 (40%), median of PRL - 594 µIU/mL [66-2880].
In group 3: hyperprolactinemia before surgery - 8 (53%), median of PRL - 572 µIU/mL [114-1650], after surgery - 8 (53%), median of PRL - 604 µIU/mL [109-1485].
Out of 18 patients with the transected pituitary stalk , hyperprolactinemia was detected in 7 (38%) cases.
CONCLUSION. The high incidence of hyperprolactinemia is caused by the localization of the CF. There was no increasing of the incidence of hyperprolactinemia among patients after the transection of the pituitary stalk. Among ventricular craniopharyngiomas the incidence of hyperprolactinemia remained at the same level after surgery.

Abstract-ID: P02-07
INCIDETENTAL HYPOHPISIS SUPPORTED BY HYPO- AND HYPERPROLACTINEMY

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Purpose of the study. Identify the frequency of occurrence and features of changes in the pituitary gland, accompanied by hypo- and hyperprolactinemia.

Materials and methods. A total of 1458 patients were examined. Patients are divided into 3 groups: 1) 161 patients with hypoprolactinemia(hypoPRL), 2) 1119 patients with normoprolactinemia 3) 178 patients with hyperprolactinemia(hyperPRL). The determination of PRL, follicle stimulating (FSH), and luteotropic (LH) hormones was performed by electrochemiluminescent mnemoanalysis on an Elecsys 2010 device (Japan), reagents by F.Hoffman La Roche Ltd (Germany). CT / MRI of the pituitary gland was performed (adenoma, incidentalomas, hernial protrusion of the arachnoid membrane were revealed). The received data was processed using the STATISTICA for Windows system (version 5.11).

Results of the study and discussion. HypoPRL - level of PRL less than 136 mIU / ml, hyperPRL - level of PRL more than 835 mIU / ml. The threshold level of HyperPRL for men was 900 mIU / ml, and for women - 1000 mIU / ml, the risk of pituitary adenoma increased. Syndrome of "empty" Turkish saddle "(PTS) was detected with HypoPRL in 23.53% of women; HyperPRL - in 2.5% of women. The pituitary adenoma was detected in HyperPRL in 60% of women. HypoPRL, PTS syndrome was detected more than 20% in women and men, and in HyperPRL of the pituitary adenoma - more than 80% in women and men. HyperPRL is detected with hormonal inactive ("mute") adenomas of the pituitary gland in case of their spread suprasellar, compression of the pituitary and hypothalamus legs and prolactin secretion.

HypoPRL, there was a change in the pituitary gland - PTS, with complaints of phobias (95.45%), autonomic crises and migraine (100%), edema (70.45%), hirsutism (29.5%); Amenorrhea (68.18%), absence of pregnancies (86.36%), interruption of pregnancy at term up to 8 weeks (80%). hyperPRL revealed a change in the pituitary gland, an adenoma of the pituitary gland, which complained of a galactorrhea (57.5%), phobias (100%), autonomic crises (97.35%), migraines (96.4%), edema (94.6% %), Hirsutism (38.9%); Dysmenorrhea (65.4%), absence of pregnancies (79.2%), termination of pregnancy after 15 weeks (96.9%).

Conclusions: In case of impaired prolactin secretion, timely computer diagnostics of the pituitary gland is necessary, which allows revealing organic changes in its structure.Pituitary incidents of more than three millimeters in diameter are detected in almost 20% of the subjects.

Abstract-ID: P02-08
PREVALENCE OF HYPEROPROLACTINEMIA IN 25-45 YEARS OLD RUSSIAN POPULATION

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Objective: to study the prevalence of hyperprolactinemia (HP) in adult Russian population aged 25-45 years and its relationship with the metabolic state and female reprodactive fanction.

Materials and methods: representative sample of Russian population age 25-45 years old has been examined in large industrial center – Novosibirsk, totally 1330 people. General examination was carried out including measurement of anthropometric parameters (height, weight, weist, BMI), blood pressure level, collection of clinical simptoms of common chronic deseases and estimation of female reprodactive fanction. Blood samles for biochemical and hormonal studies were also collected. Fasting serum glucose, total cholesterol, HDL cholesterol, triglycerides levels were measured. Presence of metabolic syndrome was assessed using Russian national criterion (2009). Level of prolactin (PRL) in blood serum was measured in 254 people representing the randomly

selected subsample of men and women using conventiolal immunoenzematic assay. Hyper- and hypoprolactinemia was assissed using manufacturer reference values: 1,8 - 17,0 ng / ml for men, 1,2 - 19,5 ng / ml for women. Data were analyzed using standard statistical analysis methods.

Results: Level of PRL was measured 156 women (35.15 ± 5.9 years) and 98 men (34.77 ± 5.9 years). The level above the upper reference values was found in 18 (7.1 %) persons. In sex groups HP was detected in 14 women (9.0 %) and 4 men (4.1 %). PRL level below reference values was detected in 7 mev (7.1 %). The average age of women with HP was 36.6 ± 6.6 years, 35.5 ± 3.3 years in men with HP and 38.5 ± 4.7 years with HP. There were no association of PRL level with metabolic syndrome (EINF 2009) and its components. Thyroid gland deseases were detected in 5 (35.7 %) of women with HP. No association between HP and female reproductive fanction was observed.

Conclusions: The prevalence of HP in adult Russian population aged 25-45 years is 7.1 %. The value above upper reference baudary was detected more frequently in women then in men. The signs of thyroid gland deseases were found in 35.7 % of women with HP. No association between PRL level and metabolic syndrome components was observed as well as female reproductive function parameters.

Abstract-ID: P02-09
EXOM SEQUENCING OF PATIENT FROM FAMILY WITH IDIOPATHIC HYPERPROLACTINEMIA

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Idiopathic hyperprolactinemia (iHP) is diagnosed after exclusion of functional prolactin level increase on the background of normal hypothalamic-pituitary region MRI. Genetic mechanism of this inherited condition is poorly understood. We report here the results of exom sequencing in one member of family with iHP. iHP was diagnosed in 5 relatives in 2 generations, including 2 women and 3 men, who had persistent hyperprolactinemia without obvious clinical manifestations. All possible iatrogenic causes of this condition and other endocrine diseases were excluded. MRI of the brain and ultrasound of the pelvic organs in female patient index case were also normal. Maximal individual prolactin level in this patient was as high as 120 ng/ml with reference values for used assay - 3.6-13.4 ng/ml. Exom sequencing information was used for further bioinformatic analysis.

First, genetic variation of genes involved in the regulation and secretion of prolactin was analyzed, namely: prolactin releasing hormone receptor (PRLHR), prolactin receptor gene (PRLR), the dopamine receptor type 2 gene (DRD2), the pituitary transcription factor gene (POU1F1), and Janus kinase (JAK 2) gene. Potentially functionally SNPs were detected for further analysis, particularly rs1613448 (CC) in the PRLHR gene; rs4988462 (CT) in the POU1F1 gene; rs2230722 (CT) and rs2274649 (AT) in the JAK2 gene; rs6276 (CT) and rs6277 (AG) in the DRD2 gene.

Discussion. The exom sequencing of 23 years old woman with a family history of aggregation of high prolactin level, without abnormalities in the reproductive system, was performed for the first time. Potentially functionally variation in genes involved in the regulation and secretion of prolactin were detected. It is necessary to determine the presence of these variants in all family member and to study further the polymorphism of the genes of other metabolic pathways that can play a role in the development of idiopathic hyperprolactinemia.

Abstract-ID: P02-10
NAD(P)-DEPENDENT BLOOD LYMPHOCYTES DEHYDROGENASES ACTIVITY IN ACROMEGALIC PATIENTS WITH PROLACTIN CO-SECRETION: POTENTIAL CLINICAL IMPLICATION

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GH and PRL, both activate STAT5 and STAT3, regulate plastic and synthetic intracellular lymphocytes process and may cause tumor growth in acromegaly. Aim: to study the NAD- and NADP-dependent dehydrogenases activity in blood lymphocytes of patients with active acromegaly with/without PRL co-secretion. **MATERIALS AND METHODS.** Total of 88 patients with active acromegaly, mean age 50,4±12,58 years, including 26 (29,54%) with PRL co-secrition were enrolled in the study. The activity of glycerol-3-phosphate dehydrogenase (Gly3PhD), glucose-6-phosphate dehydrogenase (Glu6PhD), lactate dehydrogenase (LDH), NADH-glutamate dehydrogenase (NADH-GDH), NADPH-glutamate dehydrogenase (NADPH-GDH), NAD(P)-isocitrate dehydrogenases (IDH), NAD(H)-malate dehydrogenases and glutathione reductase (GR) were measured using of biochemiluminescence method. The concentrations of serum GH, IGF-1, PRL were assessed by ELISA. **RESULTS.** Compared to control both, with/without PRL co-secretion active acromegaly patients have decreasing the activity in all studied oxidoreductases: NAD-IDH, NAD-GDH, MDH ($p<0.001$). Our results indicated that chronic excess of GH/IGF-1 in acromegaly associated with the significantly decreasing of Glu6PhD ($p<0.001$), GR ($p<0.001$), NADH-GDH ($p=0.005$) and NADPH-GDH ($p<0.001$). Compared to the acromegaly patients without PRL co-secretion, in active acromegaly PRL co-secretion group we revealed the significantly low activity of reverse-LDH ($p<0,01$) and -MDH ($p<0,05$). In active acromegaly patients without PRL co-secretion we revealed the reverse interaction between GH and NADH-GDH activity ($r=-0,52$, $p=0,014$), IGF-1 and NADPH-GDH activity ($r=-0,56$, $p=0.007$). In PRL co-secretion active acromegaly group there were interaction in pairs of PRL/GR activity ($r=+0,47$,$p=0.03$) and basal IGF-1/LDH activity ($r=+0.42$, $p=0.03$). **CONCLUSION**. High levels of PRL in acromegaly further exacerbates the negative effect of GH/IGF-1 on intracellular metabolism of lymphocytes. The increasing activity of GR in blood lymphocytes of patients with acromegaly depending of PRL level is the sign of glutathione-dependent antioxidant system insufficiency. Thus, the role of GH/IGF-1 and PRL excess in neoplastic complication of acromegaly should be studied further.

Abstract-ID: P02-11
HYPERPROLACTINEMIA IN WOMEN OF FERTILE AGE FROM ECOLOGICALLY UNFAVOURABLE TERRITORIES OF THE KYZYLORDA REGION OF THE REPUBLIC OF KAZAKHSTAN

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Goal. Estimation of hyperprolactinemia (HP) in women of fertile age from ecologically unfavorable territories of Aral Sea region, Kazakhstan and its connection with reproductive health.

Materials and methods. The study was provided within the framework of the Scientific and Technical Program "Comprehensive Approaches in Health Management of Aral Sea Region residents" in 2014-2015 years.

The representative sample of 379 women was examined with following inclusion criteria: informed consent, age 18 to 49 years, residents of Aral Sea region for 5 years at least.

Prolactin and thyroid-stimulating hormone (TSH) was measured with "Evolis" Robotic System using "ELISA-Prolactin, 67-726 mIU/l", "Tiroid-EIA-TTG, 0.23-3, 4 μIU/ml" in the laboratory of the KSMU. Reference values was used by the recommendation of manufacturer Alkor Bio (Russia). Two groups was formed based on the level of prolactin: group 1 (n = 345, mean age 36.98 ± 8.73 years), with prolactin concentration less than 726 mIU/l; group 2 (n = 34, 36.28 ± 8.39 years) with prolactin concentration more than 726 mIU/l. Gynecologic history was analyzed in each group (childbearing number, abortions, miscarriages, menstrual disorder, infertility).

Results: HP was found in 9% of women, combination of TSH more than 3.4 μIU/ml and HP above 726 mIU/l was determined in 2.6%., From the first group 62.3% - gave birth, 16.2% - had miscarriages, 2.6% had NMC, 0.89% had primary infertility. The level of TSH above 3.4 μIU/ml was determined in 35.6% of women. In the second group, 58.8% had childbirth, 11.8% had miscarriages, 2.9% had infertility. Elevated TSH was defined in 29,4%. The combination of increased TSH and GP was found in 2.6% of women, 50% of them had births, 20% had miscarriages, menstrual disorder and infertility were not observed.
Conclusion. hyperprolactinemia was defined in 9% of women. Combination of increased TSH and GP was found in 2.6% of women. Every third woman has elevated TSH. There was no significant difference in reproductive health status in women with hyperprolactinemia and normal HP.

Abstract-ID: P02-12
FEATURES OF A CLINICAL FLOW AND DIAGNOSTICS OF PATIENTS WITH THE FAMILY ANAMNESIS OF INACTIVE ADENOMAS OF HYPOPHYSIS

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The research objective was to study features of clinical semiology, their value for differential diagnostics in population of patients with the sporadic and family IAH anamnesis.

Materials and methods. The inspection included 71 IAH patients with intracellar adenoma of a hypophysis. According to a goal and research problems patients with IAH were divided into two alternative groups: the 1st group-50(70,4%) patients with environmental factors without the burdened family anamnesis and 2nd-21(29,6%) with the burdened family anamnesis, including with a panmiksiya-9(2,7%) and an inbriding-12(16,9%) patients.

At the same time the greatest number of the arrived IAH patients to fall on age from 35(23,9%) to 40(25,4%) years and to a lesser extent be elderly to 30(18,3%) and 55(5,6%) and is more senior than years that will be coordinated with literary data. It should be noted that at patients of 2-group with hereditary IAH signs is more often than at patients of 1-group-without hereditary signs prevail frequency of clinical signs, such as sexual violations - 26,5%, decrease in sight-for 40,2%, headaches-for 26,5%, doubling in eyes-for 15,0%, visual discomfort-for 12,5%, olfactory violations-for 19,8%, vegetative crises-for 12,3%, on duration of a disease among women till 5 and 20years-for 12,3 and 24,6%, but to a lesser extent till 20 and more than 21years-for 23,2 and 15,2%, and among men

of such difference it is not revealed. Undoubtedly, on frequency of clinical symptoms of a IAH disease the sizes of a tumor influenced. In the analysis of frequency of complaints in 1-group on visual violations it is revealed, decrease in visual acuity at IAH patients with a tumor to 10mm at 10% surveyed, to 20mm-70,0%, with huge-100%, at patients of 2-groups-50,0%, 87,5% and 72,7%.

Therefore, the carried-out clinical researches showed that at patients in population between with the sporadic and hereditary is IAH there are features, both on severity of a clinical current, and on terms of identification of symptoms of a disease.

At patients with the family it is IAH the main clinical symptoms of a disease associate:

-visual, sexual, headaches, vegetative crises, a climax come aged till 20-25years, and time of establishment of the diagnosis-10-20years;

-adenomas> 10mm which progress quicker, in huge adenomas, with the heavy course of a disease more often come to light, than at patients from the single is IAH;

-the IAH family form and development of clinical symptoms at early age should be object of diagnostic screening and be considered as one of modifying factors of emergence of this disease.

Abstract-ID: P02-13

EVALUATION OF CLINICAL FEATURES IN PATIENTS WITH HYPERPROLACTINEMIA DIAGNOSED BY DIFFERENT LABORATORY METHODS.

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Introduction: Macroprolactinemia is a lab phenomena when the concentration of big-big isoform of prolactin (PRL) exceeds 60% of the total serum PRL concentration. The “gold standard” technique for the diagnosis of macroprolactinemia is gel filtration chromatography. Nowadays, a new method of direct monomeric prolactin measurement is available in clinical practice but its performance versus the “gold standard” is to be established.

The aim of the study was to compare two methods of monomeric PRL evaluation.

Materials and methods: The study included 37 patients with hyperprolactinemia (3 of them were males). The mean age was 33 [17;64] years. We evaluated clinical features of hyperprolactinemia in conjunction with measuring the monomeric PRL levels by two methods: immunochemiluminescent method (Cobas 6000) with manual PEG (ICM+PEG) precipitation and immunofluorescent method (Brahms Kryptor compact plus) (IFM).

Results: The mean values of monomeric prolactin levels measured by ICM+PEG were 461.6 [375.0;821.2] mU/l, by IFM – 449.9 [357.2;749.2] mU/l. Causes of disease was detected in 9 persons (4 – prolactinoma, 2 – endometriosis, 3 – polycystic ovary syndrome). Main complains among patients were secondary amenorrhea (11.1%), galactorrhea (13.5%), oligomenorrhea 46.0%), infertility (35.1%). By MRI examination 20 patients had normal brain/pituitary appearance, 6 – microadenomas, 3 – Rathke’s cleft cysts, 2 – heterogenic appearance of pituitary, 5 – macroadenomas, 1 – “empty” sella. Treatment with dopamine agonists was received by 24 patients. The mean period of treatment varied from 1 to 36 months (mean 3.8, cabergoline mean dose 0.2-3.5 mg, bromocriptine dose 0.625-2.5 mg).

Macroprolactinemia was revealed in 12 patients (32.4%) by ICM+PEG. Among such patients 4 complained of oligomenorrhea, 3- infertility, 2 had no any disease implications, others – complex of mentioned above signs. By IFM "real" hyperprolactinemia confirmed in 4 of them, in 1 case patient had oligomenorrea and infertility, 2 – only oligomenorrhea or infertility and 1 had no complains. All persons didn't have any MRI pathology.

In 8 patients with increased PRL levels after ICM+PEG, normoprolactinemia was revealed by IFM. As for clinical features 2 persons had oligomenorrhea and 2 - infertility. MR-signs of microadenoma presented in 3 persons, heterogenic appearance of pituitary in 1, and 4 patients didn't have any MRI pathology.

Conclusions: Patients with macroprolactinemia and mild hyperprolactinemia are the most important category for using of alternative to PEG laboratory methods because a lot of disputable results and nonspecific clinical signs. Immunofluorescent method may be useful for such patient category for minimizing of incorrect treatment.

Abstract-ID: P03-01
ASSESSMENT OF EFFICIENCY OF CABERGOLINE IN TREATMENT OF INACTIVE PITUITARY ADENOMAS

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Inactive pituitary adenomas (IPA) are benign hormonally inactive pituitary adenomas which are the most difficult form of brain tumors in terms of diagnosis and therapy.

Taking into account mentioned above, **aim** of the study was assessment of effect of treatment of patients with IPA with tumors sized more than 1 sm in diameter (macroadenomas) using prolonged dopamine agonist "Cabergoline" as a primary treatment for 24 months.

Materials and methods. 78 patients who did not require urgent surgery and those who refused operative treatment were included into the study (43 men – 55.1% and 35 women – 44.9%). Cabergoline treatment was started with a dose of 0.25 mg every 72 hours in the evening with food intake with subsequent increase in 2 weeks to 0.5 mg every 72 hours, further dose was increased to 0.5 mg every 48 hours. Treatment proceeded for 24 months with dynamic out-patient follow-up in 6, 12 and 24 months. During dynamic visits the general condition, drug side effects were estimated, patients were examined by neuroophthalmologist. Fields of vision were estimated in all patients prior to the beginning of therapy and in 6,12 and 24 months in patients having initial disorders of fields of vision. Thus, by results of treatment patients were divided into 4 groups: 1) the group of patients, in which tumor size decreased by 50% from initial – 34.6%; 2) the group of patients, in which tumor size decreased by 34% from initial – 21.8%; 3) the group of patients in which tumor size decreased by less than 18% from initial – 26.9% and 4) the group of patients, in which tumor sizes did not change after 6 months of treatment – 16.7%.

Thus, primary medicamentous therapy of patients with IPA with Cabergoline may lead to reduction of tumor size, reduction and disappearance of headaches. The obtained data allow to recommend appointment of medicamentous therapy in the absence of absolute indications to surgical treatment in the maximum dose for the minimum period of 6 months with subsequent decision of issue on duration of therapy, and can be used as an alternative therapy in patients who have contraindications for or refuse surgery.

Abstract-ID: P03-02
D2 AND OX1 OREXIN RECEPTOR INTERACTION IN MECHANISM OF THE HYPOTHALAMIC SELF-STIMULATION

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The orexin (hypocretin) family of hypothalamic neuropeptides has been participated in reinforcement mechanisms relevant to both food and drug reward. There are dense concentrations of orexin receptors in the extended amygdala and mesocoricolimbic structures implicated in drug reinforcement processes.
The purpose was to clear if SB-408124, an antagonist of the orexin A OX(1) receptors, injected into the extended amygdala structures could interact with antagonist D2 receptor sulpiride on inhibition of reinforcing effects of amphetamine on hypothalamic self-stimulation in rats.
Methods. The 64 Wistar male rats were implanted bipolar electrodes into the lateral hypothalamus to study self-stimulation reaction in the Skinner box. Simultaneously, the microcannules were implanted into the central nucleus of amygdala (CA), bed nucleus of stria terminalis (BNST) or nucleus accumbens (NA) to inject the drugs studied (1 µg in 1 µl). Antagonist of the OX(1) receptors SB-408124 was administered into CA, BNST or NA, and antagonist of D_2 receptor (-)sulpiride was injected ip.
Results. SB-408124 injected into the CA, BNST or NA alone had no effect on hypothalamic self-stimulation. Sulpiride only in low dose (5 mg/kg ip) did not affect both the spontaneous and amphetamine-activated self-stimulation (1 mg/kg ip, +37-52%). Amphetamine-induced stimulatory effects were reduced by injections of SB-408124 into the BNST > NA > CA. Simultaneous administration of SB-408124 and sulpiride (5 mg/kg) inhibited amphetamine-induced self-stimulation in more degree than SB-408124 alone, that was SB-408124 potentiated the inhibitory effect of sulpiride.
Conclusion. The findings suggest that the combined use of low doses of D2 antagonists (like sulpiride) and antagonists of the orexin A-selective receptors OX(1) are necessary to reorganize the central mechanisms underlying the addiction state to target correction of addictive disorders.

Abstract-ID: P03-03
GHRELIN AND OREXIN ANTAGONISTS MODULATE EXTRAHYPOTHALAMIC CRF ACTIVITY IN RATS

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CRF is the primary activator of the hypothalamic-pituitary-adrenal axis (HPA) via anterior pituitary CRF1 activation, leading to increased ACTH secretion that stimulates glucocorticoid production and release from the adrenal gland. Increased level of blood glucocorticoids exerts negative feedback control on the HPA axis at several levels, including modulation of CRF-producing neurons. CRF also tightly interacts with peptidergic regulation. CRF not only regulates HPA axis activity, but also functions as a neurotransmitter in extrahypothalamic brain regions. CRF in the amygdala, bed nucleus of the stria terminalis (BNST), and septum has been implicated in the integration of emotional responses to stress. These studies examined the role of ghrelin and orexin in regulation of stress-induced dynamics of extrahypotalamic CRF in amygdala.

Methods. 46 male Wistar rats were the subject of the investigation, n=10-12 in each group. 36 rats were exposed to a single acute psychotraumatic situation by placing them into the cage with a hungry tiger python. The python devoured a rat in the presence of 11 others, after that the stress reaction was started increasing up to 9-10 days according to behavioral and biochemical signs. The first experimental group received SB-408124 (Sigma, USA) 10 μg/20 μl, a selective orexin 1 receptor antagonist, intranasally for 7 days. The second group received [D-Lys^3]-GHRP6 (Sigma, USA) 10 μg/20 μl, a ghrelin receptor antagonist, too. The third group and control rats received a physiological saline. After that, all rats were decapitated and the amygdala samples were taken for hormonal immunoassay. The ELISA immunoassays were carried out using EK-019-06 Corticotropin Releasing Factor (CRF) EIA Kit (USA).

Results. The experimental investigation included the quantitative determination of CRF in the homogenized rat amygdala tissue after acute psychotraumatic exposure and neuropeptide antagonists administration. The CRF level was reduced in stressed rats (439±73 pg/mg protein vs 612±10 pg/mg protein in control). Intranasal administration of SB408124 recovered it up to 576±9 pg/mg protein. Intranasal administration of [D-Lys^3]-GHRP6 also tended to recovery of CRF level in amygdala (482±91 pg/mg protein).

Conclusion. Predator induced acute psychotraumatic stress decreases the CRF level in the rat amygdala. Intranasal administration of selective orexin 1 receptor antagonist SB408124 recovered it closely to normal. Administration of ghrelin antagonist [D-Lys^3]-GHRP6 does not significantly change the CRF level in amygdala. So, there is a feedback between extrahypotalamic CRF and orexin, but not ghrelin system.

Abstract-ID: P04-01
QUALITY OF LIFE OF WOMEN WITH GRAVES' DISEASE UNDERGONE RADIOIODINE THERAPY

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Objective: To evaluate the quality of life of women undergone radioiodine therapy for the diffuse toxic goiter (DTG).
Materials and Methods: 94 women were surveyed; the control group consisted of 15 women (16.0%), the study group - 79 (84.0%) patients with DTG. Among the patients of study group undergone radioiodine therapy, 7 (8.9%) received low doses (2-4 mCi), 20 (25.3%) - the average doses (5-7 mCi) and 52 (65, 9%) - high dose (8-10mCi). After radioiodine therapy depending on thyroid function patients were divided into 2 groups. The first group included 23 patients in euthyroid state (mean age 33.1±5.74 years), the second – 56 women with hypothyroidism (mean age 35.5±5.93). Women of the control group were of similar age (30.5±5.04 years).
To assess the quality of life of patients we used the short version of the health questionnaire (MOS 36-Item Short-Form Health Survey - MOS SF-36).
The obtained data were processed using computer software Microsoft Excel, STATISTICA 6 and Biostat.
Results: The analysis of the questionnaire data showed a decline in physical health component by 26.3-35.2% compared to the control group. After radioiodine therapy there was a significant increase in all indicators of physical health component of QoL. Comparative Analysis showed that QOL in patients achieved euthyroid state was significantly higher comparing to that of women with hypothyroidism.

Prior to radioiodine therapy psychological component of health has also been reduced in the study group by 23.2-31.9% compared to the control group. 1 year after the radioiodine therapy there was a significant increase in all indicators of psychological health component of QoL in both groups. Comparative analysis of the quality of life of women from groups with eu- and hypothyroidism showed that the former were less prone to anxiety and depressive disorders.
Conclusions. Thus, women with Graves' disease decrease both physical and psychological components of QoL. Patients in euthyroidism was characterized with the best quality of life.

Abstract-ID: P04-02
CEREBROSPINAL FLUID RHINORRHOEA (CSF RHINORRHOEA) AFTER PRIMARY TREATMENT OF GIANT PROLACTINOMAS USING DOPAMINE AGONISTS

Denilbek Ismailov

Background: Currently, pharmacological therapy with dopamine agonists (DA) is considered as a treatment of choice in prolactinomas. Giant prolactinomas respond to the dopamine agonist therapy in most cases and shrunk in the first months of treatment. Rare but dangerous complication of conservative therapy of invasive prolactinoma is CSF rhinorrhoea.

Material and methods: We present a retrospective analysis of 15 patients who received DA for macroprolactinoma and developed CSF leak. All patients underwent surgical closure for CSF leak in the Institute of Neurosurgery from 2005 to 2015 and were primary administered the dopamine agonists. All patients had giant tumors. The goal of surgical treatment was to close the defect endoscopic and to resect the tumor when possible.
Results: From 2005 to 2015, 15 patients (8 men, 7 women) with giant prolactinoma underwent surgery in the Institute of Neurosurgery for to CSF leak.
The transnasal repair of the skull base defect was done in all patients, and simultaneous resection of tumor was performed in 13 of 15 patients. After the remaining resection, the repair was carried out using autofat, fascia and glue (8 cases). In rest cases, along with autofat, fascia and glue, we used a pedicled nasoseptal mucosal flap and autobone. Follow-up in was obtained 14 patients. Only one case CSF leak recurred.

Conclusion: conservative treatment of patients with giant prolactinoma must be performed under regular monitoring by ENT specialists and neurosurgeons to diagnose and to treat surgically the cerebrospinal fluid rhinorrhoea on time.

Abstract-ID: P04-03

NEUROENDOCRINE COMPLICATIONS OF RADIATION THERAPY FOR PITUITARY SOMATOTROPINOMAS

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The purpose of the study: to examine the incidence of neuroendocrine complications after RT of pituitary somatotropinomas.

Materials and methods. 30 patients surveyed after receiving RT at a dose of 45gr in 25 fractions a day. Of these, 21(70%) females, 9(30%) men. The age of patients ranged from 36 to 71

years. 37% of them had pituitary macroadenoma with para-, supra-, infrasellar growth. Duration of illness was on average 15 years. Period of observation after RT averaged 10 years.

The levels of GH, IGF-1, PRL, TSH, LH, FSH, fr.T4, cortisol, estradiol, testosterone, CT/MRI of the brain covering pituitary, visual field and acuity tests, fundoscopy were assesed.

All patients received RT in combination with drug therapy. 6 of them (20%) received RT on the background of drug therapy, 11(37%) after the TAG and 13(43%) were primary. To assess the consequences of RT we checked all parameters before (I group) and a year or more after RT (II group).

Results of the study. The following impairments took place in I group: increased GH (M=107), IGF-1(M=1138) in 75%, and hyperprolactinemia in 33%; hypogonadism in 80%, hypothyroidism in 17% , hypocorticism in 10%, decreased visual acuity in 30%, menstrual disorder in 62%, impaired potency in 11% of patients.

Group II showed the following results: GH(M=33) and IGF-1(M=434) in 38% , hyperprolactinemia in 9%; hypogonadism in 80%, hypothyroidism in 30% , hypocorticism in 50%, menstrual disorder in 67%, impaired potency in 33%, decreased visual acuity in 57% of patients.

Moreover, 20% developed ESS, 3% necrosis of brain tissue.

Conclusions. RT in pituitary somatotropinomas leads to the stabilization of the pathological process.

Abstract-ID: P04-04

TRANSSPHENOIDAL SURGERY OF NASAL LIQUORRHEA IN DRUG TREATMENT OF PROLACTINOMAS

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Prolactinomas are the most spread hormone-secreting pituitary adenomas which account for about 60% of all hormone-active tumors. Sustained-release agonists of dopamine (Dostinex) allow to achieve normal levels of prolactin and decrease a tumor size in the majority of cases. However, some cases with large tumors taking dostinex may develop nasal liquorrhea. It is conditioned by appearance of areas of bone destruction of the Turkish saddle and anterior cranial fossa due to decrease of a tumor size. In such cases there appear indications for a neurosurgical intervention.

During 2006-2016 there were 7 cases with nasal liquorrhea which had been a complication of conservative therapy with prolactin. A transnasal approach was performed. Two patients underwent repeated operations caused by a liquorrhea relapse. Cisternography revealed defects in the sphenoid sinus and posterior cells of the ethmoid bone in 6 and 1 cases respectively. Safe removal of an accessible tumor was followed by sealing of a liquor fistula in all the cases. It was made with the help of Tachocomb and one of the glues (DuraSeal, Tissucol, Evicel). A fragment of autogenous fatty tissue was used as an additional means in 5 cases.

A positive postoperative effect was watched in all the cases. It manifested itself in arresting liquorrhea and decease of prolactin levels in blood. However, all the patients under discussion had to continue taking Dostinex because of persistent hyperprolactinemia. Two cases subjected to plasty with Tachocomb and the aforementioned glue had a liquorrhea relapse in 3 months. It disappeared after treatment cancellation and resumed when these patients began to take optimum doses of Dostinex again. This situation demanded repeated transsphenoidal operations and plasty with

fragments of fatty tissue. There was no liquorrhea in a subsequent period despite treatment with dopamine agonists.

Thus, nasal liquorrhea being a complication of conservative treatment with prolactin can be reliably arrested by endoscopic transsphenoidal plasty with Tahocomb and a fragment of autogenous fatty tissue fixed by the bioglue. Use of own fatty tissue promotes formation of good adhesions in the sinus cavity. It is of great importance for cases who continue to take Dostinex against the background of further decease of a tumor mass. It is expedient either to refuse from this drug or to prescribe its smaller doses for a period of 1-2 postoperative months. It will accelerate scarring in a plasty area and decrease a threat of liquorrhea recurrence.

Abstract-ID: P05-01

THE CASE OF PREGNANCY OF 27-YEARS OLD WOMEN WITH DRAMATIC HISTORY OFOPERATED ACTH-DEPEND CUSHING SYNDROMEAND ADRENALECTOMY.

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Aim – to study the case of pregnancy of 27-years old women with operated ACTH-depend Cushing syndrome and adrenalectomy.

Materials and methods. We evaluated 27-years old married women with this diagnosis.. Her history of disease was start after married in 2007 year, when her periods stopped, she began to have complaints on arterial hypertension, obesity, stria, plethora etc. Patient was hospitalized to our clinic and we established at her diagnosis.. She was agree to do transnazal selective adenomectomy of korticotropinoma only after 2 years, in 2009 year. During 2009-2014 years she was not has any administrations. But her disease not be achieved compensation, that is why she was operated in 2015 year – adrenalectomy by right side. After this `operation we explained to patient that her possibility pregnancy may be very dangerous for her. During all years after first operation she has dismenorrheya and anovulation. After second operation patient's mother in law could receive consultation of gynecologist without us and after stimulation of ovulation patient was pregnant in spring 2016 year. She has very difficult delivery time in special hospital.

Patient always underwent clinical and biochemical evaluations including endocrine check, lipids profile, hormonal profile in 14 day of menstrual cycle (ACTH, LH, FSH, prolactin, cortisol, free testosterone, estradiolum, progesterone, etc), genitalia ultrasonography, control of height, weight, BMI, questioning and other studies.

Results. Hormonal profile showed anovulation during long time(mean LH ranged 8,7±1, 2 mIU/L, FSH 6,4±1,5 mIU/L, ACTH 56,7±1,5 mIU/L, cortisol higher 800 nmol/l) and higher range of free testosterone levels (mean 3,6±0,3 ng/ml). She had central obesity with BMI > 35 kg/m^2. WC was in normal range 104,3 ± 7, 4 cm, HC = 85, 6 ± 5,3 cm, whereas waist-hip ratio > 1, 22. Blood tests showed dyslipidemiya.

Conclusion. This young fertile-age women with operated ACTH-Cushing syndrome and adrenalectomy could achieve pregnancy after 10 years of disease because for her and very higher family traditional motivation, which wishes to have children was very dangerous for patient N.

Abstract-ID: P05-02

"THE SUCCESSFUL HISTORY OF THE FERTILITY FUNCTION IN 40-YEARS OLD MEN WITHNELSON SYNDROME AND PITUITARY SURGERY"

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Aim – to study the reproductive function in patient after pituitary surgery with ACTH-depended Cushing Syndrome, complicated Nelson Syndrome.

Materials and methods. We evaluated 40-years old married men X. with long history of ACTH-depend Cushing syndrome. He was born in Tashkent, in 1977 year. His history of disease was start in 1989 year during pubertal period., when his growth was stopped and he began to have complaints on arterial hypertension, obesity, stria, plethora etc. Patient X in age 12 yeas was hospitalized to Center of Surgery in Kiev (Ukraine) and after observation there was diagnosed ACTH-depend Cushing Syndrome. Unfortunately, he was operated step by step - bilateral adrenalectomy. During following years 8 he are receiving replacement therapy by corticosteroids and his disease achieved compensation, but in age 20 years Nelson syndrome was developed. He was married in age 20 years old and after 1 year in his family was born first his child. After 1 year patient X had been operated (transnazal pituitary adenomectomy) in Sankt-Petersburg Clinic of Neurosurgery.

Patient N always underwents clinical and biochemical evaluations including endocrine check, lipids profile, hormonal profile, control of height, weight, BMI. Nowadays he has 3 children.

Results. The patient's hormonal profile shows normal range of LH, FSH, ACTH, cortizol, testosterone). His MRI of pituitary now is normal. He are receiving Cortisone 25 mg twice per day, sometimes includes Cortineff 0,1 mg.

Conclusion. This men with operated ACTH-Cushing (Nelson) syndrome and bilateral adrenalectomy could achieve successful fertility after 28 years of disease thanks for replacement therapy only corticosteroids.

Abstract-ID: P05-03
MANAGEMENT OF PROLACTINOMAS: DIFFICULTY OR EASILY

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Introduction. The clinical manifestations of hyperprolactinemia are relatively few and usually easy to recognize. Hyperprolactinemia could be caused by prolactinomas, which are benign tumors of the lactotroph cell. Prolactinomas are more amenable to pharmacologic treatment than any other kind of pituitary adenoma because of the availability of dopamine agonists, which usually decrease both the secretion and size of these tumors. For the minority of prolactinomas that do not respond to dopamine agonists, other treatments must be used. Here we present clinical case where the noncompliance in the management of prolactinomas had led to surgical treatment without any indications.

Clinical case. Woman, 34 y.o. was presented with complaints to increase weight to 15 kg for the last 6 months, severe headaches, impaired attention and memory. It was found out from medical history that patient marked menstrual irregularity at 2007. She was consulted by gynecologist, early menopause was diagnosed, but treatment wasn`t prescribed. Pain and poor discharge in the breast

was appeared at 2011. Fibrous mastopathy was diagnosed by mammologist., symptomatic treatment was prescribed without improvement. Patient with same complaints was consulted by endocrinologist at February 2012, increased level of prolactin was revealed (800 ng/ml). Microadenoma (7 mm) was founded on MRI. So, Prolactinoma was diagnosed, dopamine agonist was prescribed (0,25 mg twice a week). Complaints was disappeared, level of prolactin was normalized after 3 months. However, patient was stopped treatment on here own and the same complaints were came back at November 2012. So, patient was consulted by neurosurgeon, which performed proton therapy of prolactinoma. Further, patient was became pregnant and was gave birth to a child at 2013. The child was on natural feeding. In 2015 the same complaints was came back, also visual impairment was appeared. Patient was consulted by endocrinologist, increased level of prolactin was revealed (120 ng/ml). Macroadenoma (12 mm) was founded on MRI. So, dopamine agonist was again prescribed (0,25 mg twice a week). Complaints was disappeared, level of prolactin was normalized (22 ng/ml) after 3 months.

Conclusions. This clinical case demonstrates that noncompliance in management of prolactinomas leads to false surgical treatment, while effective medical treatment was stopped and prolactinoma was increased.

Abstract-ID: P05-04

TEMOZOLAMIDA USE IN AGGRESSIVE MACROPROLACTINOMA. OUR EXPERIENCE IN TWO CASES

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Prolactinomas are the most frequent functional pituitary tumors. In most cases there is clinical response to dopamine agonists, a small percentage become resistant while others develop an aggressive behavior. Temozolomide (TMZ) is an agent that in some studies has shown promising results. We present two cases treated with this drug.

3. A 41-year-old male at the beginning of TMZ treatment. The diagnosis of macroprolactinoma was established at age 29, in context of visual loss (17x16x15mm and baseline prolactin (PRL) 10.016mU/ml). Cabergoline (CAB) was started, initially lowering PRL up to 200mU/ml and halving tumor size, as well as achieving visual recovery. After 3 years PRL levels started to rise and tumor growth. Surgery was indicated, and the histological analysis showed a neoplasm composed by chromophobe cells with atypia and Ki67 of 7%. After surgical debulking, PRL once again rose despite intensive medical treatment with CAB 4 mg/week and bromocriptine (BC) 2,5 mg/24 h. TMZ was started, with an initial dose of 400 mg/24h, 5 days per month, shrinking size and maintaining PRL serum values for a span of 3 years, when once again tumor growth was observed. The patient has been reoperated, plus radiotherapy as adjuvant

treatment (54Gy). After 39 cycles of TMZ, our patient is still on treatment with stable tumor remnants, but still high PRL serum levels.

4. A 27-year-old female at the beginning of TMZ treatment, diagnosed with macroprolactinoma at age 19 in context of secondary amenorrhea (40mm and baseline PRL 13171mU/ml). Initial clinical response to CAB therapy was poor, despite doses of 4mg/week. Our patient underwent transsphenoidal debulking surgery; the histological analysis demonstrated acidophilic adenoma-type cells, and Ki67 of 6-7%. Afterwards, PRL remained above control objectives despite CAB 4mg/weekly and BC 5mg daily, so radiotherapy was indicated (46Gy), as well as TMZ. She has received 20 cycles of TMZ (400mg/24h for 5 days per month) in a span of two years. A recent MRI scan showed a tumor remnant of 8x11x12mm, with adequate PRL serum levels.

TMZ is an alternative therapy in prolactinomas with aggressive behavior and lack of clinical response to conventional treatment. In our experience, TMZ seems to achieve better results; it is still unclear, in patients with long life expectancy, the optimum length of treatment.

Abstract-ID: P05-05

PROLACTINOMA ASSOCIATED WITH RECURRENT GRANULOMATOUS MASTITIS: A RARE PRESENTATION

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Granulomatous mastitis is a rare, chronic inflammatory breast disease that mimics inflammatory breast carcinoma. Although most granulomatous mastitis cases show association with oral contraceptive use, pregnancy and lactation, the exact *etiopathogenesis* is not known. We report a case of recurrent granulomatous mastitis that occurred in a patient with macroprolactinoma.

A 34 year-old woman was admitted to our department with complaints of headaches, amenorrhea and galactorrhea, accompanied with acromegalic features for the last nine years. She had three pregnancies, and all her children were breastfed. She was never on any oral contraceptives or antidepressant therapy. She had transsphenoidal surgeries for pituitary macroadenoma six and three years ago at another hospital. Her MRI showed she still had residual giant pituitary macroadenoma (sella turcica involvement, extrasellar and cavernous sinus extension, and invasion into the nasopharynx). After transsphenoidal debulking surgery, treatment with dopamine agonist and octreotide was begun. Immunohistochemical evaluation confirmed prolactin and focal GH expression. Fifteen months later she underwent radiation therapy. Octreotide therapy was discontinued 4 years later, but cabergoline treatment was continued.

Nine years after her diagnosis of macroadenoma, she noticed tender breast mass with localized erythema on the right breast. On physical examination there was a hard mass. The serum prolactin level was normal. A breast ultrasound demonstrated multiple abscesses, and she was referred to a surgeon who incised and drained purulent fluid from the breast abscesses. Six years later, she again noticed progressive pain, swelling, induration and diffuse erythema of the left breast. Ultrasound showed marked inflammatory changes in the breast. She underwent excision of the inflammatory breast mass. The biopsies were reported again as granulomatous mastitis.

Relationship between prolactin levels and granulomatous diseases have been examined, and to date, prolactinoma was identified in only seven out of 250 cases, suggesting contribution of prolactin to

physiological and pathological granulomatous lesions. Further investigation is needed to uncover the link between hyperprolactinemia and granulomatous mastitis.

Abstract-ID: P05-06

EFFICACY OF CABERGOLINE IN MALE WITH GIANT PROLACTINOMA

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This case demonstrates the management of giant prolactinoma in young male with dopamine agonists.

The 37-year-old Caucasian man was presented with intense headache and progressive visual deterioration and diagnosed with giant prolactinoma with severe extrasellar extension and involving right cavernous sinus (max. size of 70 mm) 12 months ago. The condition was complicated by bitemporal hemianopsia, latent secondary adrenal insufficiency, hypogonadotropic hypogonadism and secondary hypothyroidism. At the time of diagnosis patient's serum prolactin level was 17090.0 µg/L (4.0-15.2). After initial evaluation cabergolin therapy with a gradually increasing dose was started as well as replacement therapy with levothyroxine.

Follow-up visits was performed every 3 months. Serum prolactin level significantly decreased during one year of cabergoline therapy: 17090.0 - 10849.0 - 469.4 - 198.1 - 113.7 µg/L (4.0-15.2). Cabergoline was incrementally dose adjusted on the basis of prolactin level up to 4.0 mg per week (1.0-2.0-3.0-4.0 accordingly). Repeated MRI was performed 6 months after starting treatment, which revealed tumor shrinkage up to 25%. Despite dramatic decrease in serum prolactin level, patient remain hypogonadic (total testosterone 2.1 nmol/l) at 9 months after initiation of initial evaluation and testosterone replacement therapy was started.

Twelve months after initiation of cabergoline treatment patient lost 13.0 kg (BMI 31.3->27.1 kg/m2) and noted completely regression of headache, improvement of visual function and increase libido. Size of prolactinoma decreased to 45 mm in maximum diameter according to control MRI.

Our observation implies that treatment with dopamine agonists might be effective even in cases with giant prolactinomas. Doses of cabergoline and duration of therapy correspond with the literature data (Shimon I, et al., 2016). Regression of hypogonadism is not clearly associated with normalization of serum prolactin level in male with giant prolactinomas and may require long-term testosterone replacement therapy.

Abstract-ID: P05-07

POLYCYSTIC OVARY SYNDROME

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Background:

Polycystic ovary syndrome (PCOS): is a complex of endocrinal and metabolic disorders, the pathogenesis of which remains poorly understood. PCOS is heterogeneous clinically and

biochemically. It has 4 phenotypes: classical PCOS, hyperandrogenic PCOS (which can be associated with oligomenorrhea or anovulation), ovulatory PCOS and PCOS without hyperandrogenism.

Clinical case

A 40 years old woman came to a doctor complaining of menstrual disturbances and infertility. She has oligomenorrhea from November 2015 and secondary infertility for about 11 years. She didn't use contraception methods and has regular sexual intercourse. Her husband has no medical problems.

Menstrual history: menarche in 12 years, irregular cycles (absence more than 40 days), duration 3-5 days, LMP: 01/02/2016

Obstetric history: G1, P0, A1

Physical examination findings: BMI 23.8kgm2 (H:170cm, W:69kg), acne vulgaris, hirsutism grade 4 (according to mFG score)

Gynecological findings: by PV exam: the left adnexa is felt enlarged (diameter 5cm) and tender. The right adnexa is not felt.

Laboratory findings: Sex hormone binding globulin -19,4 nmol/L (34,3-147,7 nmol/L); free androgens index -8,4% (0,5-7,3); Serum 17-hydroxyprogesterone level -7.38 nmol/L (follicular phase: 0.4-2.1 nmol/L, luteal phase: 1.0-8.7 nmol/L) DHEA-sulfate-392,2 µg/DL (average age 35-44 years: 74,8-410,2 µg/DL); thyroid-stimulating hormone (TSH)-1,1441 ulU/ml (0,35-4,94 ulU/ml); prolactin-240,39 mIU/ml (108,78-557,13 mIU/ml).

*Serum 17-hydroxyprogesterone and DHEA-sulfate were measured in the 7th day of the menstrual cycle.

Ultrasound findings: In the left ovary, there are signs of chronic anovulation. Left ovarian volume is 17.4 ml (normal 10 ml). It has 4 follicles measuring 16x13x11 mm, 18x10x10 mm, 11x13x12 mm, 11x13x12 mm in diameter (normally: 2 to 9 mm). The right ovary has normal features.

The number of follicles that can be detected by the ultrasound, depends on its probe sensitivity. In our case we used ultrasound probe with 8 MHz and the criteria of AE-PCOS Society.

According to the patient's history information, physical examination and laboratory findings we could think about classical type of PCOS (oligomenorrhea, biochemical hyperandrogenism (FAI=8,4%), polycystic ovaries by ultrasound), although there were no clinical manifestations of hyperandrogenism.

Conclusion:

The diagnosis of PCOS is based on the presence of 2 of the three criteria (presence of chronic anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries by ultrasound findings). We should remember that there are 4 phenotypes of PCOS, that could be represented by different combinations of these symptoms. In our case, there was no definite signs of hyperandrogenemia, but it was hidden in the laboratory findings. Good analysis is very important to avoid wrong diagnosis and overdiagnosis of PCOS.

Abstract-ID: P05-08

A CASE REPORT OF AN INVASIVE GIANT PROLACTINOMA EXTREMELY SENSITIVE TO LOW-DOSE CABERGOLINE TREATMENT WITH RAPID TUMOR SHRINKAGE COMPLICATED BY CSF RHINORRHEA

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Introduction: Prolactinomas are the most common pituitary tumors, and dopamine agonists are an effective first-line treatment in most cases. Giant prolactinomas (≥4 cm) are rare (2–3%), usually present in men, and are often accompanied with very high prolactin levels, that may be resistant to medical treatment.
Case report: A 42-year-old man presented with headaches, decreased libido, gynecomastia, and several episodes of absence seizures. MRI brain revealed a large mass (44x80x51mm) involving the pituitary sella that invaded the whole sphenoidal sinus and both cavernous sinuses, with extension towards the posterior fossa. There was massive suprasellar expansion up to foramen of Monro, compressing the optic nerves and chiasma. Serum prolactin was markedly elevated at 32 000 mcg/l (normal: 4–15.3 mcg/l) and associated with hypogonadotropic hypogonadism (serum testosterone: 1.4 nmol/l, LH <0.1 IU/l, FSH 1.0 IU/l). Thyroid, adrenal, somatotrope and posterior pituitary function was normal. Cabergoline was commenced with initial dose of 0.125 mg/week with a rapid fall in serum prolactin (6937 mcg/l within 4 weeks). With further dose titration to 0.25 mg/week, and thereafter finally to 0.5 mg/week, prolactin levels continued to decline (up to 930 mcg/l at 26 weeks). Repeat pituitary MRI scanning demonstrated a progressive reduction in tumor volume. This was, however, complicated by CSF rhinorrhea due to an osteo-meningo sphenoidal defect caused by the expansive tumor mass. The patient was referred to a neurosurgeon and promptly operated. A transnasal partial resection of prolactinoma with repair of CSF rhinorrhea was performed. Pathology studies revealed a prolactin secreting pituitary adenoma, Ki67 1%. An increase in post-operative prolactin levels was observed (3253 mcg/l) and cabergoline treatment was restarted.
Conclusion: Medical therapy with dopamine agonists can be an effective strategy for giant prolactinomas. Careful supervision in cases with locally invasive tumors might decrease the risks of complications caused by rapid changes in adenoma volume with even low dose dopamine agonists.

Abstract-ID: P05-09

PROLACTIN-SECRETING PITUITARY CARCINOMAS (3 CASE REPORTS).

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According to the WHO histological classification (2004), "pituitary carcinoma" is a tumor originating from adenohypophysis cells with craniospinal and/or systemic metastases. Pituitary carcinomas make up < 0.2% of all pituitary tumors. Among all patients operated in N.N.Burdenko Center for Neurosurgery within 2000 - 2017 prolactin-secreting carcinomas were marked in 3 cases.
Case report 1. A 41-year-old woman with extrasellar pituitary adenoma and prolactin (PRL) level of 2539 mU/l underwent surgery twice with an interval of 4 months. However, a rapid and progressive

tumor growth resulted in increased brain stem symptoms, impaired respiratory function and death in the early postoperative period. Histology confirmed a PRL-positive tumor with a high proliferation index of 21% (using the Ki-67 antibody). Brain meninge autopsy revealed multiple metastases of the PRL-secreting carcinoma.

Case report 2. A 56-year-old man had surgery twice in 2005 and 2007 for a cabergoline-resistant giant prolactinoma (Ki-67 -21%). Despite surgical treatment and cabergoline therapy (4.5 mg per week), the level of PRL remained > 172000 mU/l and MRI demonstrated continues tumor growth. In 2007 patient underwent stereotactic irradiation with the following cabergoline treatment resulted in the stabilization of the tumor size. In 2017 a femoral neck fracture was diagnosed and multiple metastases in the bones and lymph nodes were detected by Positron Emission Tomography. Inguinal lymph nodes puncture confirmed metastasis of PRL-secreting carcinoma. Currently, therapy with temozolomide is being taken.

Case report 3. A 36-year-old man with extrasellar prolactinoma was operfated three times (1998-99), followed by a course of radiotherapy. In 2000 increased level of PRL> 10000 mU/l was revealed; the patient shortly received bromocriptine therapy. From 2003 to 2015 he didn't consult doctors, and no MRI was performed. In 2015 transcranial removal of PRL-secreting pituitary tumor metastasis in the parietal region (Ki-67 -10%) was followed by stereotactic radiotherapy. PRL-level after surgery was 62500 mU/l. At the same time, cabergoline therapy (2 mg per week) was started, PRL level was decreased to 430 mU/l. Repeated MRI revealed no tumor recurrence or complication within the next 2 years.

Abstract-ID: P05-10

KI-67 LABELING INDEX DECREASE BY CABERGOLINE TREATMENT IN PATIENT WITH GIANT MACROPROLACTINOMA (CASE REPORT).

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Introduction. Surgery of giant prolactinomas has been the basic method of treatment, consisting of a two-stage tumor removal (transcranial and transnasal approaches with an interval of 3-4 months between surgeries) in the pre-cabergoline-era.

Case report. A 30-year-old man with a giant macroprolactinoma (60x38x29 in size), prolactin (PRL) level>5000 mU/l (75-475) underwent transcranial removal of the suprasellar tumor part in 2003. Histology confirmed a PRL-positive tumor with a Ki-67 labeling index (LI)- 8% (according to the morphological WHO classification (2004) - regarded as "atypical" pituitary adenoma) with a strong expression of dopamine D2 -receptors. After surgery the patient received 1 mg of cabergoline per week, there was a PRL level reduction to 3800 mU/l. Control MRI performed in 4 months revealed the residual tumor, which was removed by the transnasal approach. PRL level after surgery was 1304 mU/l. Histology confirmed a PRL-positive tumor with a strong expression of dopamine D2 – receptors; but Ki-67 LI dropped to 2% (according to the morphological WHO classification - regarded as "typical" pituitary adenoma). Subsequent cabergoline therapy (0.5 mg per week) resulted in persistent normoprolactinemia, normalization of testosterone level. MRI within a 7 – year follow-up demonstrated no tumor growth.

Conclusion: Cabergoline can result in the proliferative tumor index decrease. Originally «atypical» tumor was regarded as «typical» after cabergoline treatment.

Abstract-ID: P05-11

PATHOLOGICAL GAMBLING: THE COST OF DOPAMINERGIC STIMULATION IN THE TREATMENT OF PROLACTINOMAS?

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Treatment with dopamine agonists (DAs) has been associated with neuropsychiatric side effects such as impulse control disorders (ICDs - e.g. pathological gambling, compulsive shopping, hypersexuality and binge eating) both in patients with prolactinomas but also in patients with Parkinson's disease and restless leg syndrome. We report a case of a giant-prolactinoma in a young male adult that developed severe pathological gambling under DAs. The patient presented initially with tinnitus. The magnetic resonance imaging revealed a large, invasive pituitary tumor with a diameter of 60 x 60 x 65 mm with an intracranial frontal part and perifocal oedema of the white matter. The diagnosis of the prolactinoma was based on an enormously high prolactin value of 10.000 ng/ml (normal range up to 25 ng/ml). As first line treatment the patient received bromocriptine. Under 40 mg of bromocriptine the prolactin level fell to 1.258 ng/ml and then 684 ng/ml but rose again up to 1189 ng/ml. Even under 60 mg daily, neither imaging nor laboratory improvement could be documented so that quinagolide was initiated. Under quinagolide the tumor shrank to 52 x 40 x 23 mm and prolactin fell to 298 ng/ml. After at least two years of treatment with DAs and at the age of 21 the patient was admitted in a psychiatric clinic due to pathological gambling. He had started playing with gaming machines and in online casinos, gave up his studies and lost about 10.000 German Mark in one day. He used the credit cards of his father and used to play – even if he won – until all the money he had was gone. He was sentenced to a prison sentence of 1 ½ years and later on to another sentence of 5 ½ years due to fraud and other criminal acts in order to collect money. In that time, he accumulated private debts of about 200.000 Euro. Remarkably, there was no family history of impulsive or affective behavior or further psychiatric diseases. The patient did not abuse alcohol or other illegal drugs or medications.

These observations do emphasize the rare but possible ICDs that can have devastating consequences in these patients' and their families´ lives. Taking into consideration these consequences, awareness of these rare but distinct ICDs by the treating physician but also the patient should lead to considerations of cessation of DAs on time and considerations of alternative treatment options such as pituitary surgery.

Abstract-ID: P05-12

AN UNUSUAL CASE OF IDIOPATHIC HYPERPROLACTINEMIA

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We report an extremely unusual case of idiopathic hyperprolactinemia worsening over the years and unresponsive to cabergoline treatment. A 39 year-old woman complained of oligomenorrhea and galactorrhea since she was younger. She had an uneventful pregnancy at the age of 30 years followed by repeated spontaneous abortions and infertility. Biochemical data showed high prolactin (PRL) serum levels 2517 uUI/ml (n.v.102-496) that remained elevated after polyethylene glicol (PEG) precipitation 624.10 uUI/mL (n.v. <296). Biochemical assessment of pituitary function demonstrated a condition of hypogonadotropic hypogonadism secondary to hyperprolactinemia. Iatrogenic causes of hyperprolactinemia were excluded. No pituitary tumor was found after gadolinium-enhanced magnetic resonance (3 Tesla MRI) scan of the brain. As other potential aetiologies, renal and hepatic failure and chest wall diseases were also excluded. Therefore she was diagnosed with idiopathic hyperprolactinemia and carbegoline treatment was started at the initial dose of 1 tablet 2 times/week. However, over the following three months, neither reduction of PRL levels nor an improvement of the clinical picture was observed although cabergoline dose was gradually increased up to the maximum tolerated dosage (1 tablet/daily). Perivascular epithelioid cell tumor, uterine myoma, ovarian tumor, mesocolic perivascular epithelioid cell tumor, undifferentiated bronchogenic carcinoma and hypernephroma have been described as possible sources of ectopic prolactin secretion. In order to rule out this hypothesis, whatever rare it may be, the patient underwent abdomen and thorax CT scan and Ga^{68}labelled PET/CT, both of which were negative. Cabergoline was discontinued after four years of treatment, because of the persisting hyperprolactinemia, and the patient has not received any treatment for the last year. PRL serum levels remain elevated 3332.90 mIU/ml (n.v. 56-278), causing amenorrhea, while the cause of hyperprolactinemia is still unknown. This case gives rise to new questions on unknown possible causes and management of cabergoline-resistant hyperprolactinemia.

Abstract-ID: P05-13

IS HYPERPROLACTINEMIA ALWAYS AN INDICATION TO DOPAMINE AGONIST TREATMENT?

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Pituitary tumor was diagnosed in 27-years old female patient S. by gynecologist. The patient S. complained on amenorrhea and galactorrhea. Anamnesis: three early term abortions, last pregnancy proceeded with interruption threat ended with childbirth of full-term girl with body weight 3100 grams. Lactation was absent. The daughter was 4-years old on time of patient address to the doctor. Laboratory data revealed hyperprolactinemia 1125 mUI/l, bioactive prolactin was 680 mIU/l, macroprolactin was 445 mIU/l. MRT revealed pituitary microadenoma (4x5x6 mm) which was evaluated by gynecologist as prolactinoma.

The patient was directed to endocrinologist. The endocrinologist paid attention to xeroderma, puffiness and paleness of icterus face and suspected hypothyroidism. Laboratory data revealed free thyroxin level was 4,0 pmol/l (reference range10,0-25,0), TSH 42 microIU/ml (reference range 0,23-4,5), thyroid peroxidase antibody 520 IU/ml (reference range 0-30).

Endocrinologist suspected functional prolactinoma taking in consideration both diagnosed manifest hypothyroidism and few elevated prolactin level. Hyperprolactinemia occurs in 40% patients with primary hypothyroidism and usually disappear due to replaceable therapy using thyroid hormones. The pathogenesis of hyperprolactinemia in primary hypothyroidism is caused by elevated thyroliberin level as decreasing of thyroid hormones level in blood results in hypersensitivity of pituitary lactotrophes to thyroliberin. The other possible mechanism of hyperprolactinemia is decreasing of hypothalamus dofamine releasing and decreasing of lactotrophes sensitivity to dofamine as well as decreasing of dofamine receptors amount on lactotrophes surface.

The patient S. was treated using levothyroxine on dose 1,7 micrograms per 1 kg of body weight during 18 months. Repeated MRT of brain did not visualized pituitary adenoma. This case report confirm the need of profound anamnesis collecting and inspection aimed on differential diagnostic of pituitary adenomas and adequate treatment.

Abstract-ID: P05-14

SOMATOTROPINOMA BEHIND A MASK OF PROLACTINOMA

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The female patient I., 35-years old, was directed to endocrinologist due to pituitary adenoma (prolactinoma). Anamnesis: the patient was treated from hyperprolactinemia during 10 years. Firstly, gynecologist administered cabergoline when the patient complained to primary infertility and hyperprolactinemia was revealed. Prolactin level was 1950 mIU/l (reference range up to 550) and MRT of brain visualized pituitary microadenoma. After 2 years of cabregoline treatment in dose of 1 mg in week, the patient became pregnant and gave birth the daughter. At time of inspection the prolactin level was 195 mIU/l on 0,25 mg of cabergolin 1 time in 2 week. During last 2 years pituitary microadenoma increased in 3 mm against the background of cabergolin treatment. The attempts of cabergoline dose increasing caused in sudden decreasing of prolactin level up to 25 mIU/l.

Not typical course of prolactinoma was the cause for repeated full investigation of the patient. TSH was 2,5 microIU/ml, free T4 was 12,0 pmol/l (reference range 10,0-25,0), somatotropin level was 10 ng/ml, IGF-1 level was 650 ng/ml, FSH and LH was normal. Elevated IGF-1 level allowed to suspect somatotropinoma.

Glucose tolerance test was performed using 75 grams of glucose and included somatotropin and IGF-1 levels detection every 30 min. The results showed the absence of somatotropin suppression. Somatotropin level was more than 1 ng/ml what testified the disturbances of somatotropin regulation. The patient was transsphenoidal operated in Endocrine Scientific Center, Moscow. The diagnosis of somatotropinoma was histologic confirmed. Remission came in post-surgery period. Pituitary hormones levels was in reference range. Diabetes insipidus syndrome was absent, menses cycle was saved, and hyperprolactinemia was stopped without dopamine analog treatment. Two years after surgical treatment the remission is continuous.

This case report confirm the need of full physical, laboratory and instrumental examination of patient with pituitary adenomas for specifications of hormonal activity and adequate treatment.

Abstract-ID: P05-15

HYPERPROLACTINEMIA IN TWO PATIENTS WITH EMPTY SELLA

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Empty sella is a hernation of the subarachnoid space into the sella turcica with displacement of the pituitary stalk, resulting in mild hyperprolactinemia. We report two patients who had empty sella and required long treatment with dopamine agonists.

CASE 1: A 35 year old man presented to our clinic with erectile dysfunction and his hormonal profile showed hyperprolactinemia (88 ng/ml, reference values up to 15 ng/ml) and hypogonadotrophic hypogonadism (FSH 3.7, LH 2.5 mIU/ml, testosterone 2.1 ng/ml (reference 3-9)). MRI imaging revealed a 1 cm intrasellar tumor with cystic component. The patient was started on cabergoline and responded rapidly biochemically and radiologically. Two and a half years after the initiation of therapy, his prolactin levels remained low under treatment and MRI imaging demonstated disappearance of adenoma and the presence of empty sella. Due to imaging changes and normalization of prolactin, cabergoline was discontinued. During the following year, the patient remained asymptomatic with normal prolactin levels. However, the second year after cabergoline discontinuation prolactin rose again up to three fold the normal level and a new pituitary MRI showed re-appearance of a 3 mm pituitary lesion and the empty sella.

CASE 2: A 39 year old woman with a history of rhinopharyngeal carcinoma treated with radiotherapy 3 years prior was referred to the endocrine clinic for galactorrhea and secondary amenorrhea of 8 months duration. Prolactin was found raised at 76 ng/ml (reference values up to 15) and hypogonadotrophic hypogonadism was also found. Pituitary MRI indicated the presence of an empty sella. She was treated with low doses of cabergoline (0.25 mg twice weekly) for nearly 1.5 years. During this period, her menses resumed and galactorrhea disappeared. As she developed hypotension, cabergoline was discontinued. However, she became amenorrheic again and complained of mastodynia and headaches. Repeated MRI was negative for a pituitary tumor, apart from the presence of the empty sella.

Conclusions: Case 1 illustrates the unusual evolution of secondary empty sella during shrinkage of a microprolactinoma and additionally the need for long-term follow up after discontinuation of dopamine agonists. Case 2 indicates that hyperprolactinemia associated with empty sella, especially in the context of head irradiation, can be troublesome and may require long term treatment.

Abstract-ID: P05-16

THE CASE OF PROLACTINOMA IN A 13-YEAR-OLD BOY

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Pediatric prolactinoma is a rare condition. We present a clinical case of prolactin-secreting pituitary adenoma in 13-year-old boy. At the age of ten he was admitted to regional hospital with complaints of visual acuity worsening and low height velocity. Neuroimaging revealed pituitary mass 38*34*19mm, serum prolactin level was 4868 mIU/l (N 60-510). Prolactinoma has been diagnosed and therapy with cabergoline was started. The boy received cabergoline (1 mg/week) for three years. During follow-up examinations visual acuity restored, prolactin level ranged from 190 to 220 mIU/l. At the age of 13 years negative dynamics of adenoma dimensions (40*34*20) with signs of chiasm involvement were revealed during MRI monitoring. The boy was admitted to our Hospital. The pituitary adenoma was surgically removed. Morphological and immunohistochemically examination showed atypical prolactin- and TSH-secreting adenoma with Ki-67 =5.2. Genetically investigation was performed due to early pituitary adenoma onset; mutation in *MEN1* was found. During additional laboratory investigation, we received elevated serum levels of parathyroid hormone (85.3 pg/ml at the upper limit of normal 65 pg/ml) and calcium (2.65 mmol/l at the upper limit of normal 2.55

mmol/l). In a few weeks surgical removal of parathyroid glands is planning. Conclusion. We present a rare case of PRL/TSH-secreting pituitary adenoma in 13 year`s old boy with genetically confirmed MEN1 syndrome. Follow-up data are needed to develop further management program.

Abstract-ID: P05-17

MACROPROLACTINOMA INDUCED BY LONG TERM ANTIPSYCHOTIC TREATMENT

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Antiphychotic drugs can induce hyperprolactinemia. We would like to present a woman who suffered schizophrenia from 25 y.o. Since diagnosis statement she took cyclodol and clopixol at different doses. After 2 years of antipsychotic treatment (27 y.o.) her menses stopped and galactorhea appeared however any investigation had not been done, she continued drugs intake. At age 45 she noticed vision disturbances, so visual fields investigation bitemporal hemianopsia revealed. Brain MRI: macroadenoma 32x36x33mm (19,008mm3) with supra-latero-infrasellar extension, suprasellar cistern and pituitary stalk were not visualized, deformation of the chiasma and bottom of the third ventricle. Initial prolactin levels were 3700 mU/l (120-540) however after sera dilution prolactin level was 156,300 mU/l ("hook" phenomena). Cabergoline 4 mg/weekly was started. After three months of treatment she reported visual improvement, prolactin levels 63,700 mU/l. After 12 months of treatment: normal visual fields, prolactin levels 13,210 mU/l, brain MRI: tumor size 24x27x26mm (8424 mm3) with supra-laterosellar extension without infrasellar component; suprasellar cistern and pituitary stalk were partly visualized, no deformation of the chiasma and the bottom of the third ventricle. After 24 months and 36 months of treatment prolactin levels were 8,320 and 3,740 mU/l, respectively. There was no further tumor shrinkage however the residual pituitary tumor was stable. On cabergoline treatment our patient had no worsening of schizophrenia.

This case demonstrates that prolactin levels should be monitored during prolactinstimulating treatment at least in case of menstrual disorders. It is difficult to suppose when macroprolactinoma started to grow however absence of clinical symptoms before antipsychotics could be consider as a sign of normoprolactinemia. In this case of antipsychotic induced prolactinoma cabergoline treatment in high doses was safe and effective with considerable tumor shrinkage.

Abstract-ID: P05-18

THE POSSIBILITY OF DOPAMINE AGONISTS TREATMENT IN PATIENTS WITH MACROPROLACTINOMAS AND OPTIC CHIASM COMPRESSION: CASE REPORT

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Introduction: The first line treatment in patients with prolactinomas is conservative therapy. However, in some cases (particularly, macroprolactinomas with optic chiasm compression syndrome) patients require surgery.

Case report: Male 37 years old, complaints for progressive visual loss, headache, erectile dysfunction, weight gain during the year. According the pituitary MRI - macroadenoma with endo-, suprasellar

growth (4,1*2,4*2,4 mm), examination of the eye - partial atrophy of the right optic nerve, a central absolute scotoma, laboratory data - prolactin more than 10000 mIU/ml, hypopituitarism (secondary adrenal insufficiency, secondary hypothyroidism, hypogonadotropic hypogonadism). The patient was treated with hormone replacement therapy (glucocorticosteroids, thyroid hormones), and therapy cabergoline 0.5 mg 2 times a week. The patient was sent to perform transsphenoidal endoscopic adenomectomy in Federal Almazov North-West Medical Research Centre.

At the time of hospitalization the patient took the treatment for 3 months. The patient noted significant improvement in vision (a month after start of treatment), reduction of headaches. According to hormonal tests, prolactin level in the dynamics decreased more than in 10 times - up to 840 mIU/ml (86-324). According to pituitary MRI 2 months after beginning of therapy the adenoma size decreased by more than 2 times. It was decided to refrain from surgical treatment and to continue conservative therapy.

Conclusions: dopamine agonists therapy can be successfully used in some patients even with a large macroprolactinomas with optic chiasm compression syndrome, in the case of achieving a rapid response to treatment - clinical improvement of visual impairments, lower prolactin levels, decrease tumor size by pituitary MRI.

Abstract-ID: P06-01
THE FERTILITY DATA IN PATIENTS WITHPOLYCYSTIC OVARY SYNDROME

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Aim – to study the fertility data in patients with polycystic ovary syndrome

Under our supervision in the department of neuroendocrinology of The Center of Endocrinology of PHM of Republic of Uzbekistan ambulatory in a period from September 2015 for July, 2016 120 patients of fertile age were inspected with polycystic ovary syndrome (PCOS).. Middle age of patients - 25,5 ± 4, 3 years. . The remoteness of disease hesitated in limits from 7 months to 9 years. 20 healthy women of corresponding age made a control group. The complex of researches, including clinical, biochemical hormonal, ultrasound investigations of uteri/ovaries, pituitary MRI was executed all patients.

Results. Patients were divided into two groups: 1 gr. - patients with primary sterility are 94 cases, 2 r. - patients with secondary sterility are 26 cases.

In a 1 group of patients with primary sterility the reliable decline of both pituitary and ovarian hormones was marked on a background hyperandroenemiya and hyperprolactinemiya. In the second group of patients the reliable decline of pituitary hormones was also educed on a background hyperandroenemiya and hyperprolactinemiya. while an ovarian function was within the limits of norm.

Conclusions. In both groups of patients took place hypogonadotropinemiya combining moderate hyperprolactinemiya and hyperandrogenemiya.Thus, the most expressed violations of the system of pituitary – ovarian function were found out in the first group of patients with PCOS with primary sterility, at that the reliable decline of the functional state of pituitary-gonads was marked, namely decline of LH, FSH, estradiol and progesterone of plasma of blood on 14 day of menstrual cycle..

Abstract-ID: P06-02
"THE FREQUENCY OF PREGNANCY IN WOMEN WITH ACTH-CUSHING SYNDROME IN REPUBLIC OF UZBEKISTAN"

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Aim – to study the frequency of pregnancy in women with ACTH-Cushing syndrome (CS) in Republic of Uzbekistan.

Material and methods. Under our supervision in the department of neuroendocrinology of The Center of Endocrinology of PHM of Republic of Uzbekistan ambulatory in a period from January, 01, 2000 to nowadays there are 234 patients of fertile age with ACTH-CS were inspected, from them 160 women and 74 men. Middle age of patients was 25,5 ± 4, 3 years. 20 healthy women of corresponding age made a control group. The complex of researches, including clinical, biochemical hormonal, ultrasound investigations of uteri/ovaries, pituitary MRI was executed all patients. All of patients were received surgery treatment of pituitary.

Results. Women were divided into two groups: 1 gr. - patients with secondary sterility are 152 cases, 2 gr. - patients with pregnancy after transnazal pituitary adenomectomy – 8 cases.

In the first group of patients with secondary sterility we found hyperandrogenemiya and hypercortizolemiya. In the second group of patients we found normal range of LH, FSH, ACTH, prolactin after surgery without replacement or stimulation therapy. 4 from 8 pregnant women have re-growth of pituitary tumor during pregnancy.

Conclusions. The fertility function in women with ACTH –CS is variable, because after pituitary surgery of 160 women 8 (5%) can achieve pregnancy without additional therapy.

Abstract-ID: P06-03
"THE FERTILITYFUNCTION IN PATIENTS WITH VARIOUS GIANT PITUITARY TUMORS"

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Aim of the research - to study fertility function in patients with giant pituitary tumors

Materials and methods. Outcomes of surgery in 34 patients (23 men and 11 women) with PA were analyzed. Age of patients at surgery was from 18 to 38 years. Mean age of patients – 28,5 years. All patients have a main problem – the decreasing of sexual function and infertility.

According to K. Thapar classification (1977), 4 patients had a corticotropinoma, 11 patients had somatotropinoma, 11 patients had prolactinoma and 8 patients 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 2014-2015 years.

Results. We found, that all patients have very low levels of pituitary hormones. (mean LH ranged 1,2 ± 0, 3 mIU/L, FSH 1,4±0,5 mIU/L, ACTH 26,3 ± 4,2 mIU/L, STH 0,3 nmol/l, TSH 1,7 ± 0, 7 mIU/L). The levels of cortisol was lower than 300 nmol/l, and we established lower range of free testosterone levels (mean 7,1±0,6 ng/ml), estradiol (mean 0,23±0,04 nmol/l), and progesterone (mean 2,2±0,03 pg/ml). That is why, we found secondary hypopituitarism and infertility in our patients before operation and after it.

Conclusions. The improving of fertility function in patients with giant pituitary adenomas can achieve by various ways, but after pituitary surgery. All patients will be need in stimulation of reproductive health.

Abstract-ID: P06-04

"THE REPRODUCTIVE FUNCTION INPATIENTS WITH ACTH- DEPEND SYNDROME AFTER PITUITARY SURGERY IN SURKHANDARYAREGION OF THE REPUBLIC OF UZBEKISTAN (RUZ)"

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Aim – to study the reproductive function in patients with ACTH-depend Cushing Syndrome in Surkhandarya region of the RUz..

Material and methods. Under our supervision in the Surkhandarya region of RUz from January, 01, 2017 to nowadays there are 15 patients of fertile age with Cushing Syndrome were inspected, from them 10 women and 5 men. Middle age of patients was 26,4 ± 4, 4 years. Four (40%) women from 10 had been ACTH –depend Cushing Syndrome (CS), another patients – ACTH no-depended CS.. The complex of researches, including clinical, biochemical hormonal (ACTH, LH, FSH, cortizoi, prolactin), ultrasound investigations of uteri/ovaries, pituitary MRI was executed all patients. Four women were received surgery treatment of pituitary (transnazal adenomectomy of pituitary).

Results. The patients were divided into 2 groups: 1 group – patients with conservative treatment – 11 cases (73,3%) , 2 group –patients with pituitary surgery – 4 cases.(36,3%).

We found hyperandrogenemiya and hypercortizolemiya. In patients ща ищер пкщгзыю After 1 year after surgery we established normal range of LH, FSH, ACTH, cortizol, prolactin in patients of 2 group, but in 1 group we didn't achieve compensation yet.

Operated women before surgery treatment had such complaints as amenorrhea, infertility, obesity, etc. After 1 year four (100%) operated women achieved pregnancy without stimulation therapy.

Conclusions. The fertility function in women with ACTH –depend CS can improve after pituitary surgery.

Abstract-ID: P06-05

HYPERPROLACTINEMIA IN WOMEN WITH REPRODUCTIVE DISORDERS

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We assessed 890 infertile women of reproductive age. Hyperprolactinemia was found in 39% infertile women (n=349; average age 28.4±5.6 years), pituitary microadenoma was found in 43 women with hyperprolactinemia (12%).

We analyzed parameters of infertile women with hyperprolactinemia (group 1) compared to infertile women without hyperprolactinemia (group 2; n = 429; average age 29±5.7 years).

Idiopathic hyperprolactinemia, as the only cause of ovulation failure, was found in 12% (n=41) of group 1 women, which is 5% of all infertile women (n=890). In 87% (n=308) women of group 1, hyperprolactinemia was combined with other diseases: tubal factor infertility (32%), PCOS (polycystic ovarian syndrome) (46%), uterine myoma (14%), endometriosis (19%).

Most often, analysis of group 1 reproductive history revealed primary infertility, anovulation and PCOS, more rarely – secondary infertility and childbirth (18%; 28%; $P\chi^2$=0.00); medical abortions rate was 25% higher ($P\chi^2$=0.00) than in group 2. Both studied groups showed high rates of pelvic inflammatory diseases (39%; 41%) and menstrual disorders (58%; 47%). We did not find differences in rates of amenorrhea (11%; 10%), oligomenorrhea (29%; 27%), opsomenorrhea (30%; 32%), metrorrhagie (5%; 4.5%), and dysmenorrhea (24%; 23%). We traced a higher rate of premenstrual syndrome, diffuse mastopathy and galactorrhea in group 1 (27%; 24% and 28%) as compared to group 2 (23%; 17% and 5% respectively ; all $P\chi^2 \leq 0.05$).

Our work showed that obesity rate was lower in group 1 than in group 2 (21.8%; 29.4%; $P\chi^2$=0.02). We diagnosed hyperprolactinemia in 51 % of PCOS group, where obesity was found in every third patient (33%), which exceeds substantially the obesity rate in women without PCOS (20%; $P\chi^2$=0.00). Our previous studies revealed high rates of PCOS (89%) in obese women (mean BMI=35.1±1.3 kg/m²) comparing with overweight women (mean BMI=26.9±1.1 kg/m²; 32%; $P\chi^2$=0.00). Rates of thyroid disorders (29%; 14%; $P\chi^2$=0.00), hypothyroidism (14%; 10%; $P\chi^2$=0.00) were found in group 1 more often.

In both groups were determined: decreased levels of estradiol on day 3-5 of menstrual cycle (37%; 36%; $P\chi^2$=0.86) and during the periovulatory period (78%; 73%; $P\chi^2$=0.33), progesterone in the luteal phase (20%; 26%; $P\chi^2$=0.43); increased testosterone (16%; 21%; $P\chi^2$=0.23); increased cortisol more often in group 1 (29%; 14%; $P\chi^2$=0.00).

Abstract-ID: P06-06
CUSHING'S DISEASE AND PREGNANCY

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Patients with Cushing's disease (CD) rarely become pregnant because of hypercortisolemia, hyperandrogenemia and-or hyperprolactinemia leading to fertility impairment. The aetiology is similar to the aetiology which has been found in non-pregnant women, but benign adrenal tumors are the most frequent reasons comparing to non-pregnant women, probably, because of aberrant adrenal receptors to LH and hGT.
Maternal and prenatal morbidity is increased in pregnant women with CD: gestational diabetes, hypertension, preeclampsia, eclampsia, miscarriage, spontaneous abortions, stillbirth and early neonatal death; besides, premature birth took place almost in half of cases.
CD can be diagnosed before or during pregnancy. Diagnostic tests for CD are less reliable during pregnancy. Small dose of dexamethasone usually cannot suppress cortisol secretion during

pregnancy, because of deteriorations in hypothalamic-pituitary relations. Plasma ACTH levels may be used for differential diagnosis of ACTH-dependent and ACTH- independent CD, taking into consideration physiological increase of ACTH during pregnancy. ACTH levels may not be suppressed in pregnant patients with adrenal CD, unlike in non-pregnant women. It is caused by placental ACTH synthesis or stimulation of ACTH by placental corticoliberin. Big dexamethasone suppression test is useful for recognition of CD and ectopic ACTH secretion.
If there is a suspicion for CD during pregnancy, it is necessary to use visualization methods (MRI) for localization of adenoma in patients planned for surgery. At decision-making concerning treatment, severity of hypercortisolemia and pregnancy degree are the important factors. Treatment of CD will be reconsidered in case of delay of fetal growth rate, and it is necessary to take into account preliminary laboratory data. A method of choice in treatment of ACTH-secreting pituitary adenomas is transsphenoidal surgery which can successfully be applied in women in the second trimester of pregnancy.
Conclusion. If CD is diagnosed in the first trimester of pregnancy, depending on severity of hypercortisolemia, medicamentous therapy is necessary up to tumor removal in the second trimester. Surgical treatment is a method of choice in treatment of CD in pregnant women in the second trimester. If CD is diagnosed in a late third trimester, medicamentous therapy is preferable, and surgical treatment should be postponed for the postpartum period.

Abstract-ID: P06-07
UNAUTHORIZED GLUCOCORTICOID TREATMENT BECAUSE OF NONCOMPLIANCE OF THE DIAGNOSTIC ALGORITHM OF HYPERANDROGENISM

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Introduction. Hyperandrogenism (HA) is a clinical syndrome of excessive androgen action on target tissues and organs of women. HA can develop because of different causes and lead to decreased female fertility. It is necessary to carry out differential diagnosis before prescription of treatment. Noncompliance of the diagnostic algorithm of HA leads to prescription of drug treatment without any indications.

The aim of this study has been to evaluate the prescription of drug treatment of HA according to the diagnostic algorithm by endocrinologists in clinical practice.

Materials and methods. A retrospective analysis of 15 case reports of women with established diagnosis of HA (mean age 28 years). The following parameters were analyzed: clinical manifestations of HA (menstrual irregularities, hirsutism, alopecia, acne), laboratory examination (total testosterone, 17OH-progesterone, DHEA-S), prescribed drugs and complications of the treatment. Hirsutism was evaluated by Ferriman-Gallwey score.

Results. All 15 women had no hirsutism (Ferriman-Gallwey score <8) and alopecia. 12 patients had not report menstrual irregularities and acne. Only 3 patients had oligomenorrhea. Thus, there were no indications for further laboratory examination in all 15 women. However, level of total testosterone was evaluated in 10 patients, that was within the normal range. At the same time, incorrect laboratory test was performed in 5 women. Nevertheless the diagnosis of HA was established, glucocorticoid treatment was prescribed. 11 patients have received methylprednisolone (daily dose 8 mg) a mean 11 months. 4 women have received hydrocortisone in daily dose of 30 mg for 6 months and 40 mg for 12 months, respectively. So, iatrogenic hypercortisolism was developed in 4 patients. The diagnosis of HA was unauthorized and it was excluded. So, cessation of the drug

were attempted to all patients. However, chronic adrenal insufficiency was developed in 2 initially healthy women, which requires life-long glucocorticoids

Conclusions. Noncompliance of the diagnostic algorithm of HA caused false diagnosis in 15 healthy women. Laboratory examination was reformed to all patients in spite of clinical manifestations of HA, and its was performed incorrectly to 5 women. As a result, unauthorized glucocorticoid treatment were led to iatrogenic hypercortisolism and chronic adrenal insufficiency in initially healthy women.

Abstract-ID: P06-08

PREGNANCY RATES FOR WOMEN WITH AMG LEVEL OF 0/9 NG/ML AND LESS IN ART PROGRAMS

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According to the ART Department of Irkutsk Regional Clinical Hospital Regional Perinatal Center providing reproductive assistance to couples from Irkutsk and Irkutsk region, Russia, in 2016, pregnancy rates (PR) per embryo transfer amounted 37.9%. However, after 35 years the PR decrease, which is caused by defective ovarian response to ovulation stimulation, impaired quality of the retrieved oocytes and their fertilization pattern up to complete absence, changes in nature of embryo cleavage rate; all these finally lead to decreased IVF results. In addition, we also observe poor reproductive response in young women of reproductive age when the number of maturing follicles is 5–6 or less, and the AMH level is less than 1.0 ng/m.

Following the results of ART programs in 2016, we have analyzed PR in 95 infertile women aged 28–46 with poor ovarian response and AMH level of 0.9 ng/ml and less. The analysis was performed in groups of women aged 28-34 (n=47, group 1), 35-39 (n=27, group 2), and 40-46 (n=21, group 3).

In women with low AMH, PR per stimulated cycle comprised 10.5%. Yet, group 1 showed higher PR (12.8%) than women of late reproductive age (group 2 (11.1%); group 3 (4.8%); $p<0.05$). We transferred embryos in 28(60%), 22(81%), and 11(52%) women from groups 1, 2, and 3 respectively. Note that in all the groups, the rates of cancelled transfers did not differ (40%; 22.7%; 47.6%). This can be explained by the fact that in late reproductive age women, the embryos transferred were not of the best quality, which is acceptable for younger patients. This is supported by the PR per embryo transfer; for women under 34, PR are substantially higher (group 1; 21.4%) than for group 2 and 3 patients (13.6% and 9.1% respectively; $p<0.05$). As result, 4 babies were born in group 1; women after 35 did not deliver, all the pregnancies were missed abortions, which again speaks for poor quality of the retrieved embryos.

Thus, the analysis showed low ART effectiveness in women with low AMH. At the age of 34 and younger, transfer of only the top quality embryos is justified for infertile women with low AMH; for women of late reproductive age with low AMH, it is inexpedient to use basic IVF protocol due to known ineffectiveness.

Abstract-ID: P06-09
CUSHING SYNDROME AND PREGNANCY: A SYSTEMATIC REVIEW INCLUDING 3 NEW CASES

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Context: Cushing's Syndrome (CS) is an uncommon disease characterized by an increased production of glucocorticoids, that left untreated can lead to serious consequences. Women with CS rarely achieve pregnancy.

Aim and Methods: Perform a systematic review of published cases of pregnancy in patients with CS by means of an extensive search on the Medline and Web of Knowledge databases. Describe three new cases observed in our institution. We compared two groups: the "active disease" group (17 pregnancies), and the "non-active disease" group (20 pregnancies).

Results: Cushing disease was the main cause behind CS (28 pregnancies). We observed 2 spontaneous abortions, 1 ectopic pregnancy in the "active" group and 2 spontaneous abortions, 1 placental abruption and 1 medical interruption of pregnancy in the "non-active" group. Within the "active" group, we reported 9 full-term and 5 pre-term pregnancies and, in the "non-active" group, 11 full-term and 3 pre-term pregnancies, 2 were non-specified. Hypertension was diagnosed in 8 cases (6 in the "active" and 2 in the "non-active" group) and gestational diabetes in 4 patients (3 and 1 in the "active" and "non-active" categories).
Discussion: A major concern refers to the medical control of CS activity, because hypercortisolism occurs physiologically during pregnancy. This is a topic with extreme clinical significance since conception is rare.

Abstract-ID: P06-10
PECULIARITIES OF ENDOCRINE PATHOLOGY DIAGNOSTICS OF PAIR INFERTILITY IN REAL CLINICAL PRACTICE

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Relevance: according to WHO, there are about 10% of infertile couples worldwide. Despite the availability of all kinds of laboratory and instrumental study methods, as well as various subsidiary reproduction technologies, the results of infertility treatment remain disappointing.

Purpose: to study the peculiarities of infertility couples diagnosis in real clinical practice.

Materials and methods: a retrospective analysis of medical documentation of 11 couples who applied to the City Endocrinology Center of the City Hospital No. 4, Rostov On Don, Russia, with the diagnosis of infertility. The following parameters were assessed: simultaneous counseling of both

partners, appointment of a spermogram study before the start of female partner's tests, assessment of ovulation in the female partner, screening for hyperprolactinaemic syndrome and subclinical hypothyroidism, androgens in women without indications (irregular menses, alopecia, hirsutism and acne resistant to dermatological therapy), the duration of the examination until the cause of infertility was established, the appointment of treatment with normal results spermogram, the appointment of dietary supplements to women.

Results: According to the analysis, the following data were obtained: i) simultaneous consultation of both partners was carried out in 1 case out of 11; II) the appointment of an examination of the spermogram before the start of female partner's examination - in 4 men out of 11 couples; III) the estimation of ovulation - in 6 women from 11 pairs; IV) screening for hyperprolactinemic syndrome - in 8 women out of 11 couples; V) screening for subclinical hypothyroidism - in 3 women from 11 pairs; VI) study of androgens in women who didn't have signs and symptoms of hyperandrogenism was performed in 10 women of 11 pairs; VII) on average, the duration of the examination until the cause of infertility was found was 3.3 years (± 1.7 years); VIII) treatment with normal spermogram results was assigned to 5 men of 11 pairs; IX) BAA intake was recommended to 7 women of 11 pairs.

Conclusion: In the vast majority of cases, infertility is not perceived as a pathology of the couple, the order of the partners' survey is not observed, most hormonal studies are performed in the absence of evidence, the examination is delayed for a year, and substances with proven inefficiency are appointed as treatment. The obtained results testify to the acute need for the creation of strict protocols for examination and management of infertile couples, as well as an interdisciplinary approach to this pathology.

Abstract-ID: P06-11

MEASUREMENT OF GLUT4 GENE EXPRESSION IN HUMAN UMBILICAL VEIN ENDOTHELIAL CELLS AT GESTATIONAL DIABETES MELLITUS

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Introduction: Gestational diabetes mellitus (GDM) is associated with increased frequency of type 2 diabetes mellitus and obesity in offsprings. This is probably a result of the epigenetic effect of intrauterine hyperglycemia. However, the mechanisms through which GDM in mother affects the development of these diseases in the offspring has not been studied well enough. According to animal studies , the level of glucose transporter type 4 (GLUT4) gene expression in adipose tissue is decreased in diabetes mellitus and obesity, which leads to insulinresistance.

Objectives: To study the effect of intrauterine hyperglycemia and its correction on the level of GLUT4 expression in human umbilical vein endothelial cells (HUVECs) of newborns from females with GDM.

Materials and methods: The study included 41 females with GDM treated for GDM starting before 30-th week of gestation (GDM1), 9 females treated for GDM after 34-th week of gestation (late treatment group or GDM2) and 17 females without GDM (control group). GDM was diagnosed according to International Association of Diabetes and Pregnancy Study Groups criteria. Umbilical cord was taken from the females immediately after delivery. HUVECs were isolated and stored in liquid nitrogen at -196 ° C. The level of GLUT4 gene expression was determined in HUVECs by real-time PCR. The expression level was normalized according to the expression of the "housekeeping" gene GAPDH.

Females with GDM kept electronic diaries of nutrition and glycemic control by means of a specially developed mobile application and sent data to the doctor. Based on the personal diaries the integral indicators characterizing the self-control of glycaemia (mean fasting and postprandial glycaemia, the frequency of exceeding the target levels of glycaemia) were automatically calculated. Statistical analysis included Kruskal-Wallis test, Mann-Whitney test and Spearman correlations.
Results: There was no statistically significant difference in the degree of GLUT4 gene expression among the groups (50.3 ± 67.0, 80.6 ±91.0, 80.4 ± 70.9, p = 0.270). The difference in age and body mass index among the three groups was statistically not reliable. There was no correlation between the degree of GLUT4 gene expression and recorded maternal levels of glycaemia.

Conclusion: There was no difference between the degree of GLUT4 gene expression among the groups of women with GDM and the control group.

Keywords: Gene expression; GLUT4; pregnancy, gestational diabetes mellitus, intrauterine hyperglycemia

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Abstract-ID: P06-12
PREGNANCY IN ACROMEGALIC PATIENS - 4 CASE REPORTS OF A REFERENCE CENTRE

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INTRODUCTION: Fertility is frequently impaired in women with acromegaly. However, pregnancy is becoming more common due to improvement in acromegaly treatment and fertility therapies.

CASE REPORTS: Herein we report the cases of 4 patients with acromegaly, with a mean age at the diagnosis of 28.8±2.5 years-old and initial IGF-1 levels of 797±318 (Reference Value 115-357ng/mL). Neuroimaging revealed 3 macro- and 1 microadenoma. All the patients underwent transphenoidal surgery. Two of the women presented criteria of cure after surgery and the other 2 needed additional treatment with radiotherapy and/or medical therapy. They became pregnant with a mean age of 35.3±2.7 years-old. Three of them conceived spontaneously and the other underwent ovarian stimulation and *in-vitro* fertilization. Only one patient got pregnant with elevated IGF-1 levels (417ng/mL). At the time of conception one of them was on dopaminergic agonist and the other on somatostatin analogues that were both withdrawn after the pregnancy diagnosis. Neither campimetric changes nor headaches that warranted neuroimaging evaluation were reported. Two of the women presented with gestational diabetes needing insulin therapy and one of them with gestational hypertension. One of the new-borns had Acute Respiratory Distress Syndrome that implied surveillance in a neonatal Intensive Care Unit in the first days after delivery, and another was

diagnosed with ureteral duplication. Currently, the patient that got pregnant after ovarian stimulation is pregnant again after a spontaneous conception.

CONCLUSION: As pregnancies in acromegalic patients are relatively rare, the analysis of such cases can help us to define the best follow-up and therapeutic options for them. In addition, a careful multidisciplinary approach is needed as some maternal and fetal complications, like pregnancy diabetes and hypertension, seem to be more frequent in these patients.

Abstract-ID: P06-13
THE ROLE OF AUTOIMMUNE THYROIDITIS IN PATHOGENESIS OF HYPERPROLACTINEMIA

Vladimir Utekhin

The most common complication of autoimmune thyroiditis (AIT) is hypothyroidism, which stimulate the processing of both thyrotropine (TSH), and prolactin (PRL), which provokes even the development of pituitary prolactinomas.

We examined 151 patients with AIT and hypothyroidism accompanied by hyperprolactinemia (HPRL): women - 119 (age 33.5 ± 1.3), men - 32 (age 30.1 ± 2, 9). 31 had obesity with rose striae. In all of them, the levels of PRL, testosterone (TS), and TSH were studied, and magnetic resonance imaging (MRT) of the pituitary gland with contrast was performed.

Prior to treatment, the PRL level in the general group was 583.3 ± 33.4 μU / ml, the TSH level was 2.8 ± 0.1 μMIU / ml, TS for men - 17,4 ± 2,27 nM / l, TS for women - 1,48 ± 0,37 nM / l. The normal MRT was registered only in 28 (18.5%) cases, adenoma - in 60 (39.7%) cases (11 of them were from 6 to 20 years old), the heterogeneous pituitary structure was in 51 (33 , 8%), the "empty" Turkish saddle - in 5 (3.3%), the cyst of the Ratke pouch - in 4 cases (2.6%), lipoma - in 2 cases (1.3%), microhypophysis - in 1 case (0.7 %). The level of PRL in prolactinomas was 683.7 ± 34.8, in cases with the heterogeneous structure of the pituitary - 522.3 ± 37.6, in those with normal pituitary - 525.2 ± 40.8 μIU / ml. The maximal level of PRL (34,390 μIU / ml) was matched in barren male of 29 years with a pituitary macroadenoma (19 × 21 × 18 mm) and a TS level of just 6.86 nM / l (after the removal of the adenoma he became the father of two children).

After 4-6 months of treatment with levothyroxine and dopamine agonists, the PRL level fell to 234.15 ± 59.4 μIU / ml ($p<0.001$), TSH - fell to 1.21 ± 0.3 μIU / ml ($p<0.001$), TS increased in men to 19 , 27 ± 3.9 nM / L ($p>0.1$) and decreased in women - up to 1.27 ± 0.33 nM / l ($p>0.1$).

Consequently, persons with AIT and HPRL need a pituitary MRT, but one should not expect for a PRL increase of up to 1000 μIU / ml. In all women with pronounced premenstrual syndrome, mastodynia and mastopathy, it is necessary to investigate the levels of thyroid hormones, TSH and PRL.

Abstract-ID: P06-14
"THE FREQUENCY OF REPRODUCTIVE DISORDERS IN WOMEN WITH ACTH-DEPEND CUSHING SYNDROME IN THEREPUBLIC OF UZBEKISTAN(RUZ) , TASHKENT-CITY AND REPUBLIC OF KARAKALPAKSTAN (RKK).."

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Aim – to study disorders of the reproductive function in patients with ACTH-depend- Cushing Syndrome in (CS) in all regions of the RUz,Tashkent city and RKK..

Material and methods. Under our supervision in the 8 regions of RUz and Tashkent-city there are 120 women of fertile age with ACTH-depend Cushing Syndrome were observed in the framework of project. . Middle age of patients was 27,6 ± 3, 4 years.

The complex of researches, including clinical, biochemical hormonal (ACTH, LH, FSH, cortizoi, prolactin), ultrasound investigations, pituitary and adrenals CT/MRI was executed all patients.

Results. The patients were divided into 2 groups: 1 group – patients with conservative treatment – 47 cases (39,1%) , 2 group –patients with pituitary surgery – 65 cases.(54,1%), 3 group – combined therapy – 8 patients (6,6%)

The reproductive disorders had 63 women from 120 (52,5%): amenorrhoea – 22 patients (35%), oligomenorrhoea -19 (30%), polimenorrhoea - 22 (35%). 57 women have normal periods.

We found hyperandrogenemiya and hypercortizolemiya. In patients of all groups before treatment. One year after surgery we established normal range of LH, FSH, ACTH, cortizol, prolactin in all women of 2 group, but in 1 and 3 group we didn't achieve compensation yet.

After 1 year only 1 (2,1)% women from 1 group can pregnant. After 1 year 30 women from 65 patients of second group after pituitary surgery (46,1%) achieved pregnancy without stimulation therapy. .There are 2 (25%) women of 3 group achieved pregnancy.

Conclusions. The fertility function in women with ACTH –depend CS can improve after pituitary surgery without stimulation therapy. In 46,1% of cases, in patients with combined therapy -in 25%.and in women after conservative therapy – in 2,1%.

Abstract-ID: P06-15

COMPLEXITY OF MANAGING PATIENTS WITH HYPOGONADOTROPIC HYPOGONADISM IN ASSISTED REPRODUCTION

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Introduction: Hypogonadotropic hypogonadism (HH) is characterized by failure in the gonadal function due to deficient secretion of gonadotropins with consequences on reproductive function.

Patients with HH requiring assisted reproductive techniques (ART) represent a therapeutic challenge for their characteristic response to ovarian stimulation (OS). The aim of the study was to evaluate the outcome of in-vitro fertilization (IVF) cycles in women with HH in terms of ovarian response and reproductive results.

Methods: We retrospectively assessed outcomes in 9 patients with HH undergoing IVF in the Reproduction Unit of Hospital 12 Octubre between 2008 and 2016. As control patients, we selected 18 patients with male or tubal factor, matched by age and date of first IVF cycle.

Results: Both groups were comparable in age, BMI and sperm characteristics. The antral follicle count was higher in control group (6.56 ± 6.93; 13.94 ± 5.68, p=0,007) which reflects the difficulty in identifying small follicles, often <5 mm, in women with HH. The number and percentage of cycles with insufficient ovarian response (<3 oocytes or E2 <600 pg/ml) was higher in the HH group (0.56 ± 0.52 vs 0.11 ± 0.47, p=0,036; 29.63 ± 34.13 vs 3.70 ± 15.71, p=0.011). The number of cycles of OS with maximum FSH starting dose was higher in the HH group (1.67 ± 1.32; 1,44 ± 0,78, p= 0.044), as well as the total FSH dose used during the OS (3673.33 ± 924.46; 2110.94 ± 743.98, p=<0.0001). The risk of ovarian hyperstimulation syndrome (OHSS) should be considered in patients with HH who often require high doses of GN: There was 1 case of severe OHSS and 1 cancelled cycle because of risk of OHSS. No differences were found in terms of the number of IVF cycles/patient, cancelled cycles, number of total embryos, embryo quality or clinical pregnancy rate.

Conclusion: IVF outcomes in patients with HH were comparable to those of control patients of same age. However, management of this patients is complex, often presenting inadequate response of OS or hyper-response with risk of OHSS making ideal FSH dose selection for OS specially challenging.

Abstract-ID: P06-16
FERTILITY OF MAN WITH A VIOLATIONS OF PROLACTIN SECRATION

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The purpose of the study. To assess the fertility of men with a violation of prolactin secretion, to develop a diagnostic algorithm for fertility indicators.

Materials and methods. 106 men separate 3 group: 1)24 men (hypoprolactinemy), age 31.75 ± 1.65, the body mass index (BMI) 24.96 ± 0.94; 2)71 men (normoprolactinemy), age - 32.21 ± 0.75, BMI 27.35 ± 0.42; 3)11 men (hyperprolactinaemy), age - 34.18 ± 2.83, BMI - 30.91 ± 0.73. Determination of hormones - prolactin (PRL), follicle stimulating (FSH), luteotropic (LH), thyrotropic (TTG) testosterone (T), cortisol (K), insulin (INS) - Elecsys 2010 (Japan) F.Hoffman La Roche Ltd (Germany). 2 groups were formed - with normal and impaired fertility.

Results of the study. In case of prolactin secretion (hypo- / hyperPRL), relative leukocytosis, a decrease in the concentration and number of sperma, a decrease in the number of mobile and normal spermatozoids, an increase in the number of immobile and degenerative forms compared with the group of men with normoprolactinemia. HyperPRL, there was a significant (P <0.05) increase in spermatogenesis cells. Significant differences (p <0.05) were found between the BMI and T. Increased levels of PRL, TSH, INS, and K and a decrease in T level were accompanied by significant disorders Fertility in patients with a BMI of more than 30%. Hypo / HyperPRL, fertility abnormalities were found in 72.96% and 84.18% of cases, respectively. In the course of statistical analysis, the main parameters affecting fertility in men were identified: parametric- BMI, PRL level, INS, sperm counts, sperm concentration, and nonparametric - CT of the pituitary gland. Each parameter was given an evaluation score. In our array of risk scores was in the range from 1 to 5. The value of "3 *" points, which can be considered as a threshold value for the diagnostic output. By the method of

constructing classification trees a value of -2.5 was obtained. The sensitivity of our algorithm is 100%, the specificity is 90.0%. The degree of the positive prognosis is 97.6%, and the negative forecast - 100%, the diagnostic accuracy - 98%. Relatively low specificity is explained by the presence of false positive results, which is quite acceptable when other pathology can have.

Conclusions: 1. Fertility impairments were found in 70% of patients with a body mass index of more than 30% if to increase the secretion of prolactin, insulin, cortisol, thyroid stimulating hormone and a drop in testosterone levels

Abstract-ID: P06-17

DIFFERENTIAL GENES EXPRESSION IN HUMAN UMBILICAL VIEN ENDOTHELIAL CELLS IN GESTATIONAL DIABETES CASES: ROLE IN CARDIO-METABOLIC DISEASES PROGRAMMING

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Background: Understanding the mechanism whereby the intrauterine hyperglycemia in women with gestational diabetes mellitus (GDM) affects the offspring' predisposition to metabolic and cardiovascular diseases may help prevent their intergenerational transmission. Our aim was to study the effect of the degree and duration of maternal hyperglycemia on the level of expression of genes associated with cardio-metabolic diseases in human umbilical vein endothelial cells **(**HUVECs) of newborns from women with GDM.
Materials and methods: HUVECs were isolated from 41 women with GDM treated for GDM starting before 30-th week of gestation (GDM1), 9 women treated for GDM after 34-th week of gestation (late treatment group or GDM2) and 17 women without GDM (control group). The level of intercellular adhesion molecules (ICAM1 and VCAM1), angiopoietin-like protein 4 (ANGPTL4), a major glycoprotein of the vascular endothelium - endoglin (ENG), mammalian tribbles homologue 1 (TRIB1), mitochondrially encoded NADH: ubiquinone oxidoreductase core subunit 2 (MT-ND2), mitochondrial transcription factor 1 (TFAM) prostaglandin-endoperoxide synthase 1 (PTGS1), mesoderm specific transcript (MEST), placenta specific 8 (PLAC8) and nuclear receptor subfamily 3 group C member 1 (glucocorticoid receptor) (NR3C1) genes expression was determined by RT-PCR.
Results: Three of the above mentioned genes were associated with GDM: ANGPTL4, MT-ND2 and TRIB1. Both GDM2 and GDM1 groups showed significantly reduced levels of MT-ND2 and ANGPTL4 genes expression as compared to the control group (9.3±5.4, 9.9±23.0 and 56.1±82.8 for MT-ND2 respectively, p=0.007, and 10.4±5.8, 22.3±25.4 and 111.4±129.1 for ANGPTL4 respectively, p=0.014), but no difference was observed between GDM1 and GDM2 groups. TRIB1 gene was differentially expressed among the three groups: 7.5±5.4, 4.9±2.9 and 2.6±0.9 in controls, GDM1 and GDM2, respectively (p=0.003). After comparison in pairs the difference was significant between GDM1 and GDM2 (p=0.0059) and between GDM2 and control group (p=0.0051).
Conclusion: The decrease in MT-ND2, ANGPTL4 and TRIB1 genes expression level has been detected in HUVECs of newborns from women with GDM compared to control group. The duration of hyperglycemia was associated only with TRIB1 gene expression that presumably confirms the role of intrauterine hyperglycemia in cardio-metabolic diseases programming. Further studies are required

to prove a cause-effect relationship between ANGPTL4, MT-ND2 genes expression and GDM respectively.
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PREGNANCY AND TUMOR OUTCOMES IN WOMEN WITH PROLACTINOMA

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Context: Management of prolactinomas during pregnancy has always been a challenge. There is a concern about the risk of tumor growth as well as the effects of the treatment on the developing fetus. Another issue is the outcome of women with prolactinoma after pregnancy and lactation.

Objective: To evaluate remission of hyperprolactinaemia after pregnancy and lactation in women with prolactinoma. To describe the safety of dopamine agonists for the fetus.

Patients and Methods: A retrospective study of 32 pregnancies in women with prolactinoma was conducted in a single-center. Other causes of hyperprolactinemia were excluded. Prolactin level was recorded at diagnosis, under treatment, and during follow-up.

Results: Pregnancies resulted in one spontaneous abortion (3.1%) and 31 live births (96.9%). No stillbirths, multiple or ectopic pregnancies or trophoblastic disease were recorded. There was only one malformation (club foot) recorded (3.1%). Twenty-three women reinitiated dopamine agonists after pregnancy.

Conclusion: Fetal exposure to bromocriptine at conception is not associated with an increased risk of adverse neonatal or pregnancy disclosures. Among endocrinologists there is considerable diversity in management of prolactinomas during pregnancy, indicating a need for better consensus and carefully follow guidelines.

Abstract-ID: P06-19
HYPOGONADISM IN PATIENTS WITH ACROMEGALY

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Introduction: Hypogonadism is a frequent consequence of acromegaly. It may even occur in patients with microadenomas, who are not at risk from hypopituitarism due to local mass effects. Prolactin and growth hormone hypersecretion contribute to the pathogenesis of hypogonadism in acromegaly but previous studies also demonstrated the presence of hypogonadism in microadenoma patients even in the absence of hyperprolactinaemia.

Aim and methods: To evaluate the prevalence of hypogonadism in patients with acromegaly seen between 1978 and 2011. Medical files were reviewed, clinical and analytical parameters were recorded. Hypogonadism was defined as amenorrhoea in women (menopause women were excluded) and testosterone deficiency in men.

Results: Information was available on 83 patients, of whom 55.4% were women. The mean age at diagnosis was 54+/-16 years. Hypogonadism was present in 33.7% globally. Seventeen women were amenorreheic, 6 of these presented low FSH and LH levels and 8 presented hyperprolactinaemia. Only 5 referred decreased libido. Twelve men presented low levels of testosterone, 9 of these with evidence of hyperprolactinaemia. Four patients with hypogonadism had microadenomas, 2 without simultaneous hyperprolactinaemia. GH levels were higher in patients with hypogonadism ($P < 0.005$).

Conclusion: Acromegaly is a rare disease with enormous consequences not only metabolically but also in terms of repercussions on other hormone secretion patterns. This can be due to growth hormone levels itself, simultaneous prolactin secretion or due to tumor mass effect.

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