rs16928751 *ADIPOR2* genes in women of the Russian population.

KEYWORDS: obesity, metabolic syndrome, genotypes of the polymorphisms.

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FERTILITY RESTORATION IN A PATIENT WITH RESISTANT PROLACTINOMA AFTER COMPLEX THERAPY OF DOPAMINE AGONIST AND SELECTIVE ESTROGEN RECEPTOR MODULATOR

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Introduction. Prolactinomas are the most common pituitary adenomas and dopamine agonists (DA) still remain the first choice of treatment. Nevertheless it does not always exert an adequate effect and endocrinologists face the challenge of resistant prolactinomas more frequently. This problem is very important for women of reproductive ages who desire to recover fertility. We present a clinical case of a woman with DA resistant prolactinoma and primary amenorrhea who had recovered regular menstrual cycle and ovulation after one year of combination treatment with cabergoline and tamoxifen. **Clinical case.** In 2002 a 12-year old woman was referred to our tertiary care center with hyperprolactinemia (prolactin (PRL) level 5000 IU/l (90—540), no macroprolactinemia) and macroprolactinoma 10×18×10 mm by MRI. Administration of cabergoline with maximum dose 3.5 mg a week did not result in significant clinical or laboratory improvement. In 2004 transnasal transsphenoidal adenomectomy was performed. Postoperative prolactin levels remained high. For short period the patient received injections of octreotide without effect. In 2006 the repeat operation was conducted because of additional tumor tissue of 8×7×10 mm on MRI. After surgery PRL decreased to 3000 IU/l, cabergoline therapy was restarted in dose 1 mg per week with gradually increasing up to 4.5 mg that allowed to stabilize tumor growth, but without recovery of menstrual cycle. During examination in 2015 PRL level was 6000 IU/l, endoparasellar adenoma visualized on MRI and hypoplasia of the uterus with the lineal endometrium were detected. As an antitumor agent, the patient was assigned a treatment with selective estrogen receptors modulator (SERM) tamoxifen — in a dose 20 mg per day in combination with cabergoline in a dose 4.5 mg per week. After one year of such therapy the prolactin was 15000 IU/l, adenoma's MR-characteristics didn't reveal any negative trend. At the same time the patient noted that menstrual function restored in 3 months after starting tamoxifen. Ultrasound examination confirmed normal uterus size and adequate endometrial thickness; also, the left ovary contained corpus luteum. The therapy was prolonged with recommendations of careful ultrasound control of endometrium state and barrier contraception. **Conclusion.** This case demonstrates reversion of symptoms of hyperprolactinemic hypogonadism in a patient with DA resistant prolactinoma due to SERM treatment without prolactin level normalization. The pathophysiological mechanisms underlying the phenomenon are not clear but may be due to the changers in interactions of kisspeptin neurons involved in GnRH secretion due to modulation of negative and positive estrogen feedback.

KEYWORDS: hyperprolactinemia, plolactinoma, tamoxifen, cabergoline.

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EPIGENETIC ASPECTS OF BONE METABOLISM REGULATION IN PATIENTS WITH ENDOGENOUS HYPERCORTISOLISM

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Objective. To investigate mRNA and microRNA related to bone of remodeling in bone tissue samples from patients with Cushing's disease (CD). **Material and methods.** Patients with clinically evident and biochemically proven active CD and patients with hormonally inactive pituitary adenoma matched by age, sex and BMI were invited to participate. Bone samples were taken during transsphenoidal adenomectomy from the base of the sella-turcica, immediately placed in lysis buffer (QIAzol) and subjected to homogenization. 24h urine free cortisol (24hUFC) was measured by an immunochemiluminescence assay on a VitrosECi (60-413 nmol/24 h). Total RNA isolation from bone tissue with on-column digestion of the genomic DNA was carried out with miRNeasy Mini Kit on the automatic station «QIAcube». Reverse transcription was carried out using a High-Capacity RNA-to-cDNA Kit. Gene expression analysis was performed by Real-Time PCR on StepOnePlus instrument with Custom TaqMan Array 48 Plus plates. MicroRNA expression analysis was carried out by TaqMan Advanced miRNA Assays. **Results.** We enrolled 24 subjects (15 patients with CD and 9 with hormonally inactive pituitary adenomas); 18 females and 6 males, the mean age was 41 years (confident interval (CI) 95% 36—46) mean BMI — 29 (CI 95% 26—32) kg/m^2. There were no significant difference between the groups. Mean 24h UFC in subjects with CS — 1168 (CI 95% 702—1634) nmol/24h. Expression of osteoblast activity and bone formation genes was decreased in patients with CD: ALPL 0.34 (CI 95% 0.24—0.43; p<0.001), BGLAP 0.41 (CI 95% 0.28—0.54; p<0.001), COL1A1 0.26 (CI 95% 0.14—0.37; p<0.001), COL1A2 0.51 (CI 95% 0.33—0.69; p<0.001), MMP2 0.52 (CI 95% 0.41—0.62; p<0.001). The expression of SOST 5.3 (CI 95% 1.8—8.8; p<0.001), WNT10B 10.24 (CI 95% 5.26—15.22; p<0.001), WNT3A 1.44 (CI 95%

0.3—2.57; p=0.016), CD40 3.5 (CI 95% 3.13—3.91; p<0.001), BMP7 2.03 (CI 95% 1.22—2.83; p<0.001) was increased in subjects with hypercortisolism as compared to inactive pituitary adenoma. An increase in the expression of microRNA 133a-3p 1,74 (CI 95% 0.14—3.34; p=0,037), that stimulate osteoclastogenesis, and microRNA 204-5p 0,54 (CI 95% 0.06—1.02; p=0.031), that block the differentiation of osteoblasts was found. **Conclusion.** Suppression of osteoblastogenesis in patients with endogenous hypercortisolism is explained by an increase in the expression of the SOST, which codes the main inhibitor of the Wnt signaling pathway — sclerostin. Reduction of osteoblast differentiation is also realized through increased expression of 133a-3p microRNA and 204-5p microRNA.

KEYWORDS: microRNA, osteoblastogenesis, hypercortisolism.

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MCCUNE-ALBRIGHT SYNDROME (MAS): CLINICAL CASE

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Introduction. McCune-Albright syndrome (MAS) — a systemic disease associated with a mutation in the gene GNAS1, responsible for the activation of a G protein subunit (Gsa), is characterized by symptoms: fibrocystic dysplasia, skin pigmentation, precocious puberty. **Clinical case.** A 29 — y. o. male patient during past 12 years noted a gradual change in his appearance. Began to seek a medical attention only 3.5 years ago due to reduced vision. Hormonal tests revealed marked elevation of GH to 106 (<20 mIU/ln), and IGF-1 to 567 (121—336 ng/ml), decrease in testosterone levels to 1.91 (3-12 ng/ml), other gormons within the reference range. MRI of the brain showed a 4×7 mm adenoma of the anterior part of the pituitary. CT brain scan with contrast described poliostic dysplasia of the skull bones. Octreotide depot injections therapy was initiated 20 mg/28 d. Than levels of GH and IGF-1 were still high in spite of medical treatment — 119 (<20 mIU/ln) and 1033 (121—336 ng/ml), respectively. At the age of 27 years the patient was 205 cm tall (BMI 29.5 kg/m^2) at admission to Endocrinology Research Centre. His facial features were acromegaloid with sloped towered skull. "Café au lait" pigmentation of the skin was noted at the chest, back, and abdomen. Lab tests confirmed the presence of the active acromegaly (GH — 117 (< 20 mIU/ln), IGF-1 — 1412 (121—336 ng/ml)). Brain MRI with contrast showed a marked increase in the size of previously described adenoma 17×23×14 mm, and progression of the fibrous dysplasia (predominantly hypointense on T1) of the skull base, parietal, temporal bones, scales of the frontal and occipital bones, hypopneuma-tization of frontal sinus and ethmoidal labyrinth, narrowing of the internal and the external auditory canals on the left. All these symptoms allowed us to suspect the MAS. The progressive clinical course of the disease, insensitivity to octreoride treatment was the basis for the choice of further surgical treatment despite the pronounced fibrous dysplasia of the skull base. Then the patient underwent endoscopic endonasal removal of tumor using navigation BrainLab at Burdenko Neurosurgical Research Institute. Postoperatively levels of GH and IGF-1 decreased to - 27 (<20 mIU/ln) and 856 (121—336 ng/ml), visual function had improved markedly. He was then followed on depo octreotide injections 30 mg/28d and cabergoline 2 mg/w with later dose adjustments. The high-performance parallel sequencing was implemented with the gene panel (*MEN1, CDKN1B, PRKAR1A, GNAS, AIP, SDHA, SDHB, SDHC, SDHD, PRKCA, CDKN2C, CDKN2A, POU1F1, PTTG2*). **Conclusions.** The treatment of acromegaly in the setting of the MAS is characterized by multiple challenges that require the participation of a team of experienced endocrinologists and neurosurgeons. This patient with the MAS was identified heterozygous p.S163P replacement in *SDHB* gene.

KEYWORDS: McCune-Albright syndrome, acromegaly, parallel sequencing, pituitary adenomas.

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OBESITY PARADOX: CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND OBESITY

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Introduction. Obesity and type 2 diabetes mellitus (T2DM) are commonly associated with cardiovascular complications. At the same time, obesity paradoxes are not new to the field of cardiovascular disease and have been observed in heart failure, acute coronary syndromes, and chronic kidney disease. **Clinical cases.** Two patients (both non-smoking men) comparable for age (48—50 years), BMI (32.1—34.4 kg/m^2) glycated hemoglobin (HbA_{1c}) (6.0—6.3%), hypoglycemic therapy (Sulfonylureas with Metformin) and diabetes duration (3—5 years) were treated in Endocrinology Research Centre during 2016 year. There was no significant differences in routine laboratory tests (total cholesterol, low-density cholesterol, high-density cholesterol, triglycerides, fasting glucose, microalbuminuria). First patient (50 years old, BMI 32.1 kg/m^2) had several cardiovascular complications at the time of hospitalization: including Myocardial infarction, coronary angiography revealed multi-vascular atherosclerotic lesion of coronary vessels (left anterior descending coronary artery, right coronary artery and circumflex artery were stenosed up to 90%) and athero-