with exogenous rhGH and there is also in vitro evidence showing a more efficient signal transduction through this exon 3 deleted isoform. Some studies have found that patients with acromegaly harboring the exon 3-deleted genotype may have a higher prevalence of diabetes and hypertension. **Hypothesis and Objective:** Patients with active acromegaly harboring the exon 3-lacking GHR genotype may have more echocardiographic abnormalities than those who are homozygous for the exon 3 containing genotype. **Patients and Methods:** This is a cross-sectional study of patients with active acromegaly, defined by an IGF-1 level > 1.3 times the upper limit of normal (x ULN), who underwent transthoracic echocardiography. Exon-3 GHR genotype was determined by PCR using previously described sense and antisense primers. **Results:** The cohort consisted of 28 patients, 54% female, with a mean age of 51 ± 12 years. Mean disease duration at the time of echocardiographic examination was 4.48 ± 4.7 years; median basal GH and IGF-1 were 12 ± 26 ng/mL and 2.4 ± 1.04 x ULN. The prevalence of hypertension and diabetes were 43% and 36%, respectively. Fifty three percent of the patients were homozygous for the exon 3-containaing genotype (+3/+3), 18% were homozygous for the exon 3-lacking genotype (-3/-3) and 29% were heterozygous (+3/-3). Clinical and biochemical features did not differ between patients with the different GHR genotypes, except for hypertension that was more prevalent in the +3/+3 genotype group (60% vs 23%, p= 0.04). The frequency of the different echocardiographic parameters was similar among groups (left ventricular hypertrophy 33% vs 15%, p= 0.27; diastolic dysfunction 47% vs 31%, p= 0.39; subclinical systolic dysfunction 42% vs 54%, p= 0.54; left ventricular ejection fraction 59±10% vs 60±16%, p= 0.83); aortic valve abnormalities 19% vs 15%, p=0.63; mitral valve abnormalities 46% vs 15%, p=0.07). **Conclusions:** Echocardiographic abnormalities in patients with active acromegaly do not differ among patients with the different GHR exon 3 genotypes. The clinical spectrum of acromegaly varies considerably. Although such variability is usually related to the severity of the hypersomatotropinemia, in many patients this is not the case.

Neuroendocrinology and Pituitary

PITUITARY TUMORS

Giant Prolactinomas: An Experience From South India

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Giant prolactinomas are large lactotroph adenomas, defined as those with maximum dimension of >4cm. They constitute <5% of all prolactin secreting tumors, and are more frequently seen in men. They present with features of hyperprolactinemia and hypopitutarism and are responsive to dopamine agonist therapies. In the current study we have shared our experience on management of giant prolactinomas over the last 15 years. We collected clinical data retrospectively from medical records of patients with giant prolactinoma managed at our institute over the last 15 years. This study describes the symptomatology, tumor characteristics and response to therapy. Our study included 21 patients with 15 males and 6 females. The mean age of presentation was 32 ± 10.3 years, ranging between 10 to 53 years. Vision defect was the predominant complaint (57%, 12 patients), followed by headache (52%, 11 patients). Erectile dysfunction was a presenting feature in 13% of men (2 patients) and amenorrhea/galactorrhea in 33% of women (2 patients). Seizure was seen in 10% of the patients (2 patients) and 10% (2 patients) were diagnosed with giant prolactinoma on evaluation for primary infertility. Tumor associated pituitary dysfunction manifested as hypogonadism in 67%, 14 patients, central hypothyroidism in 38%, 8 patients, and hypocortisolism in 1 patient. The median maximum tumor dimension was 4.4 cm with median basal PRL of 7168 ng/ml. Five patients underwent debulking surgery (24% of the patients) prior to endocrinology referral for indications such as apoplexy/raised intracranial tension. All patients received cabergoline and a mean dose of 2.1 ± 1.7 mg/week (range, 1-7 mg/week) was prescribed to attain a median nadir prolactin level of 48 ng/ml over a median period of 4 months (range, 1-40 months). The follow-up MRI data was analysed for 13 patients. Tumor shrinkage of >50% from the baseline was seen in all but 1 patient (92%) and 2 patients had disappearance of radiologically detectable tumor. Although giant prolactinomas have a greater tumor burden than the more common macroprolactinomas, the responsiveness to dopamine agonist therapy is excellent and surgical therapy is reserved for any exceedingly large tumors to relieve compression on vital structures.

Neuroendocrinology and Pituitary

PITUITARY TUMORS

Hypercoagulability in ACTH-Dependent Cushing Syndrome

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Introduction: ACTH-dependent Cushing syndrome (CS) is associated with hypercoagulability; however, the incidence and timing of thrombosis during evaluation and management of CS is unclear.
Objective: To evaluate the incidence and timing of thrombotic events in patients with ACTH-dependent CS following diagnosis and management.
Methods: We performed a retrospective, longitudinal study of patients with ACTH-dependent CS seen at Stanford University Health Care from 1998 to 2020. Thrombotic events — deep vein thrombosis (DVT), pulmonary embolism (PE), cerebral vascular accident (CVA), and myocardial infarction (MI) — were recorded between diagnosis and 12 months following therapeutic intervention.
Results: Of 108 patients with ACTH-dependent CS, 97 (89.8%) were women, and the mean age at diagnosis was 43.0 years (± 15.7 years). Sixty-eight (63%) patients had hypertension, 38 (35.2%) had diabetes mellitus, and 11 (10.2%) were active smokers. Of the 108 subjects, 97 (89.8%) had Cushing Disease (CD) and 11 (10.2%) had ectopic CS. Of the 97 patients with CD, 38 (39.2%) underwent inferior petrosal sinus sampling (IPSS), 59 (60.8%) underwent transsphenoidal surgery (TSS), 19 required repeat TSS (19.6%), and 15 underwent TSS and bilateral

adrenalectomy (BAL) (15.4%). Of the 11 patients with ectopic CS, 3 (27.2%) underwent IPSS, 6 (54.5%) underwent BAL, and 1 (9.1%) underwent TSS and BAL.
There were 10 thrombotic events among 7 (7.2%) CD patients, but no thrombotic events among ectopic CS patients. Of the thrombotic events, there were 7 (70%) DVT/PE, 2 (20%) CVA, and 1 (10%) cortical vein thrombosis. Six (60%) occurred within 30 days after TSS (range 3-25 days), 2 (20%) between 31 days and 1 year after TSS (range 59-165 days), 1 (10%) 26 days after IPSS but prior to TSS, and 1 (10%) in a patient who did not undergo IPSS or surgery. No thrombotic events were noted after BAL. Of the 8 postoperative thrombotic events, 5 (62.5%) occurred while patients received supraphysiologic glucocorticoid replacement (defined as >25mg hydrocortisone or equivalent daily) after curative surgery, 1 (12.5%) occurred after a patient was tapered to physiologic glucocorticoid replacement, and 2 (25%) occurred in patients who had persistent disease despite surgery. The degree of hypercortisolism at baseline was not associated with risk of thrombotic events. **Conclusions:** In this retrospective study, 6.5% of ACTH-dependent CS patients had a thrombotic event, all in patients with CD. The majority had venous thromboembolism with DVT/PE, and the highest incidence occurred up to 30 days after surgery. The degree of hypercortisolism at baseline did not correlate with subsequent thrombotic events. Therefore, it is important to monitor all patients with ACTH-dependent CS following surgical intervention for venous thromboembolism.

Neuroendocrinology and Pituitary
PITUITARY TUMORS

Immunohistochemical Profile of Nonfunctioning Pituitary Adenomas

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Background: Nonfunctioning pituitary adenomas (NFPAs) are neuro-endocrine tumors without clinical and laboratory signs of anterior pituitary hormonal hypersecretion. The recent World Health Organization classification is based on the adenohypophyseal cell lineages and requires immunohistochemical evaluation of adenohypophyseal hormones and pituitary transcription factors. There are few data regarding the age and sex prevalence of different cell-types nonfunctioning adenomas and clinical data correlations. **Objective:** To discover the immunohistochemical profile of large cohort of NFPAs. **Materials and Methods:** The study includes 100 consecutive cases of endoscopically transsphenoidally removed nonfunctional pituitary adenomas, immunohistochemically assessed for anterior pituitary hormones and transcription factors. Clinical presentation, imaging, laboratory hormonal data and immunohistochemical staining features have been analyzed. All patients (64 women and 36 men) have been divided into four age groups: 20-34 (A) years old, 35-44 (B) years old, 45-59 (C) years old, 60-70 (D) years old. Peculiarities of immunohistochemical profile have been statistically analyzed in those age groups. **Results:** Most tumors (97%) were macroadenomas with mass effect symptoms. In the groups of silent corticotroph and Pit-1 adenomas most of the patients had subclinical symptoms of hormonal hypersecretion. The proportions of silent gonadotroph adenomas have appeared to be increased with age with predominant prevalence in group D (60%) in women and group C (78, 6%) in men. The proportions of silent Pit-1 adenomas decreased with age with maximum rate in group A (77,8%) in women and in group A (50%) in men. The incidence of silent corticotroph adenomas was different: increasing with age in women with maximum (36,8%) in group C and decreasing from young age (30%-0%) in men age groups B-D respectively. Plurihormonal pituitary adenomas from different cell lineages were found only in women, with maximum incidence rate (17,6%) in group B. The incidence of "null cell" adenomas didn't differ in men and women in group B and C but was much more higher in men in groups A and D (16,7% vs 0% and 33% vs 6,6% respectively). **Conclusions:** The different age and sex prevalence of NFPAs, revealed in our study, may be helpful in diagnosing and optimal treatment of NFPAs.

Neuroendocrinology and Pituitary
PITUITARY TUMORS

Increased Serum High-Sensitivity C-Reactive Protein in Growth Hormone-Deficient Patients With Non-Functioning Pituitary Tumors

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Introduction: Growth hormone (GH) deficiency, the most common hormone deficit complicated with pituitary tumors, is associated with higher mortality and cardiovascular events. Inflammation, as measured by high-sensitivity C-reactive protein (hs-CRP), has been reported to be associated with cardiovascular events. However, the association between hs-CRP and GH deficiency is still unknown. We retrospectively evaluated the association between serum hs-CRP levels and GH secretion in patients with non-functioning pituitary tumors (NFPTs). **Methods:** In this retrospective study, adult patients with non-functioning pituitary adenoma (NFPA) and Rathke's cyst who received a GH-releasing pepitide-2 (GHRP-2) test from 2013 until 2016 were included. Patients with a history of pituitary surgery or radiation, or estimated GFR lower than 30 mL/min/1.73m^2 were excluded. **Results:** Of 81 patients (70 NFPA and 11 Rathke's cyst), 44% were diagnosed as severe GH deficiency by GHRP-2 test. Serum hs-CRP level was significantly higher in the male patients (P = 0.001) and the patients with regularly alcohol intake (P = 0.011) and was significantly correlated with BMI (r = 0.35, P = 0.002), creatinine (r = 0.41, P < 0.001), eGFR (r = -0.29, P = 0.009), peak GH response to GHRP-2 (r = -0.48, P < 0.001), AST (r = 0.32, P = 0.004), ALT (r = 0.34, P = 0.002), γGTP (r = 0.41, P < 0.001), HDL-cholesterol (r = -0.33, P = 0.003) and triglyceride (r = 0.25, P = 0.02). Smoking habit (P = 0.084), age (r = 0.18, P = 0.10), LDL-cholesterol (r = 0.16, P = 0.15), IGF-1 (r = -0.14, P = 0.23) and IGF-1 SD score (r = -0.11, P = 0.32) were not significantly correlated with serum hs-CRP level. Peak GH response to GHRP-2 (β = -0.24, P = 0.024) was a significant variable to determine serum hs-CRP level after adjustment for age, sex, BMI, regularly alcohol intake and serum creatinine, γGTP