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The Secret Behind Anemia in Patients With Acromegaly

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Introduction: The GH/IGF-1 axis has regulatory effects on erythropoiesis. GH deficiency is associated with normocytic anemia in adults, and hemoglobin (Hb) concentrations are normalized after GH replacement. Little is known about the significance of anemia in acromegalic patients. The aim of this study is to evaluate the factors associated with anemia in patients with acromegaly.
Methods: A single-center retrospective cohort study was conducted. A total of 381 acromegalic patients who admitted to the University Hospital from 1980 to 2018 were included. Information regarding the demographic features, the pre-operative and follow-up hormone levels, radiological features of adenoma, treatment modalities, comorbidities, presence of cancer, colonoscopy results, medication history, presence and type of anemia together with the CBC, iron parameters, 25(OH)D, and vitamin B12 levels at the time of anemia detected were retrieved from the patient record system. Anemia was defined as Hb levels <12.0 g/dL in women and <13.0 g/dL in men.
Results: Of 381 acromegalic patients (120F/98M, age: 44±13yr/45±12 yr); 218 cases (57.2%) were diagnosed with anemia (67% normocytic, 33% microcytic) at a median duration of 6 months after the diagnosis of acromegaly. Hb values were 11.1±0.9 g/dL in women and 12.1±1.0 g/dL in men. Serum levels of ferritin and transferrin saturation were lower in anemic patients (p<0.001). The levels of 25(OH)D and vitamin B12 were lower in the anemic group, but the differences were not statistically significant. Anemia was detected more likely in patients who had macroadenoma (p=0.001), suprasellar extension (p=0.001), and cavernous sinus invasion (p<0.001) on pre-op MRI and residue tumor (p<0.001) on post-op MRI. Patients with anemia had higher GH, IGF-1 and PRL levels (p<0.01), and there was a significant difference related to the use of octreotide (p<0.001). Anemia was observed more frequently in patients with a history of radiotherapy (29% vs. 10%, p<0.001). Hypopituitarism was seen in 63 (29%) patients in the anemic group and 21 (13%) patients in the non-anemic group (p<0.001). Cancer prevalence in the study population was 14.2%, and the most commonly diagnosed cancers were thyroid, bladder, prostate, and breast. Although not statistically significant, the prevalence of cancer was higher in anemic patients compared to non-anemic patients (17% vs. 10%). There was no significant difference regarding the presence of colorectal polyps between groups, and only two anemic patients were diagnosed with colon cancer.
Conclusion: This is the first study highlighting that anemia is a common comorbidity in patients with acromegaly, and that anemia can be related to characteristics of the tumor, hormonal status, type of treatment, and the presence of cancer in addition to nutritional factors. Therefore, a comprehensive evaluation is required for anemia in acromegalic patients.

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The Value of 4D Speckle-Tracking Strain Echocardiography in Evaluating the Relationship Between Asprosin and Growth Differentiation Factor-15 Levels and Subclinical Systolic Dysfunction in Patients With Acromegaly and Prolactinoma

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Introduction: In patients with acromegaly and prolactinoma, the long-term presence of elevated GH and PRL levels is associated with an unfavorable cardiovascular risk profile. Early recognition of dysfunctions related to cardiovascular complications, which can be a significant contributor to mortality, is important. The aim of this study was to assess the relationship of four-dimensional speckle-tracking strain echocardiographic (4DSTE) measurements with asprosin, GDF-15 levels, and the Framingham cardiovascular risk score (FRS) in patients with acromegaly and prolactinoma. **Methods:** The study included 41 acromegaly [20F/21M, age: 49 (41-57)], 29 prolactinoma patients [18F/11M, age: 40 (28-48)] and 33 healthy control subjects [15F/18M, age: 48 (37-54)]. Data are presented as median with interquartile ranges (IQR). Anthropometric, biochemical and echocardiographic measurements were performed. Asprosin and GDF-15 levels were measured by ELISA. **Results:** Plasma asprosin concentration in the prolactinoma group [2.4 ng/mL (0.0-9.7)] was significantly lower than the concentration in both the acromegaly group [6.8 ng/mL (2.6-9.9)] and the control group [10.2 ng/mL (2.3-18.0)] (p=0.022 and p=0.006, respectively). In the study population, asprosin levels were positively correlated with age, FRS, and GDF-15 levels (r=0.361, p<0.001; r=0.275, p=0.005 and r=0.240, p=0.015; respectively). Plasma GDF-15 concentration was lower in prolactinoma group [262.2 pg/mL (169.3-336.1)] than in the acromegaly [332.5 pg/mL (257.4-438.8)] and control groups [331.3 pg/mL (233.6-428.9)] (p=0.008 and p=0.047, respectively). In multiple linear regression analysis, GDF-15 level was independently positively related to the FRS in both patient groups (p<0.001). FRS was highest in patients with acromegaly (p=0.004). In 2DE; the left ventricular ejection fraction although within normal limits, was lower in acromegaly [63% (63-65)] and prolactinoma [63% (60-65)] patients compared to the healthy controls [66% (63-68)] (p=0.003). In both acromegaly and prolactinoma groups; global longitudinal, circumferential, areal and radial strain measurements identified by 4DSTE were lower than the control group (acromegaly: p=0.007, p=0.008, p=0.015, p=0.008; prolactinoma: p=0.033, p=0.019, p=0.030, p=0.025, respectively). In contrast, diastolic functions were evaluated as normal in 85%

of acromegaly patients, 86% of prolactinoma patients, and 93% of the control group (p=0.365). **Conclusion:** This is the first study to demonstrate the isolated subclinical systolic dysfunction identified by four-dimensional echocardiography in patients with acromegaly and prolactinoma. Asprosin may be associated with cardiovascular diseases in addition to its role in the pathogenesis of type 2 diabetes mellitus, and GDF-15 can be used as a biomarker to predict cardiovascular risk in these patient groups.

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Transcription Factor Immunohistochemistry in the Diagnosis of Pituitary Tumors

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Objective: The clinical utility and prognostic value of WHO 2017 lineage-based classification of pituitary tumors have not been assessed. This study aimed to (1) To determine the clinical utility of transcription factor analysis for classification of pituitary tumors and (2) To determine the prognostic value of improved lineage-based classification of pituitary tumors. **Methods:** This was a retrospective evaluation of patients who underwent surgical resection of pituitary tumors at a tertiary referral centre between 1990 and 2016. Included patients were at least 18 years of age and had complete histopathological data, forming the "histological cohort". Patients with at least 12 months of post-surgical follow up were included in the subgroup "clinical cohort". The diagnostic efficacy of transcription factor immunohistochemistry in conjunction with hormone immunohistochemistry was compared with hormone immunohistochemistry alone. The prognostic value of identifying "higher risk" histological subtypes was assessed. **Results:** There were 172 patient tumor samples analyzed in the histological cohort. Of these, there were 96 patients forming the clinical cohort. Subtype diagnosis was changed in 24/172 (14%) of tumors. Within the clinical cohort, there were 21/96 (22%) patients identified with higher risk histological subtype tumors. These were associated with tumor invasiveness (p=0.032), early recurrence (12-24 months, p=0.016), shorter median time to recurrence (38 [IQR 20-68.5] v 15 [IQR 12-27.25] months, p=0.02) and reduced recurrence-free survival (p=0.023). Conclusions: Application of transcription factor analysis, in addition to hormone IHC, is associated with improved diagnostic information.

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USP8 Somatic Mutations in Cushing's Disease and

Silent Corticotropinomas

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Background: Somatic mutations in the ubiquitin-specific peptidase 8 (*USP8*) gene have been described in Cushing's disease (CD). These mutations increase proopiomelanocortin transcription resulting in ACTH production and seem to correlate with somatostatin receptor type 5 (SST5) expression. Aims: Screen *USP8* in patients with corticotropinomas and correlate *USP8* mutational status with SST5 expression in CD. **Methods:** Tumor DNA was extracted and then exon 14 amplified by PCR. SST5 was assessed by immunohistochemistry (clone UMB4) and quantified multiplying the percentage of positive cells (0,0%; <10%,1;10-50%, 2; 51-80%, 3; >80%, 4) and intensity (mild, 1; moderate, 2; intense, 3), giving a score (IRS) from 0-12 with ≥ 6 considered high. **Results:** Among 59 patients, 38 had CD and 21 silent corticotropinomas. In CD, 13 (34.2%) patients had pathogenic mutations (6 had p.Ser719del; 5 had p.Pro720Arg and 2 had p.Pro720Gln). In the mutated CD group, all were women and had median age of 34.5 years (20-46). Median ACTH was 64.7pg/mL [(34.8-330.0), normal <46], urinary free cortisol (UFC) 435.0μg/24h [(87.0-1386.0), normal <100], cortisol after *overnight 1mg dexamethasone* suppression test (ODST) 17.4μg/dL [(5.0-48.7), normal <1.8], salivary cortisol (SC) 8.1μg/dL [(1.0-15.5), normal <0.35]. Median largest tumor size was 0.9 cm (0-1.9), ki-67 1.7 (0.2-10.0) and IRS 12 (1-12). In wild-type CD group, 19 (76.0%) were women and had median age was 35.0 years old (14-62). Median ACTH was 59.7 (39.0-137.0), UFC 305.8 (77.0-1302.0), cortisol after ODST 23.6 (10.0-33.3), SC 0.67 (0.27-1.28). Median largest tumor diameter 0.7cm (0-3.3), ki-67 1.8 (0.2-10) and IRS 4 (0-12). SC was higher in mutated group compared to wild-type (p=0.001) as well as IRS (p=0.009). In silent corticotropinomas, 2 (9.5%) had pathogenic mutations (1 p.Ser718Pro and 1 p.Pro720Arg): male, 36 years old, 3.2 cm tumor, Ki-67 4%, IRS 6; and female, 52 years old, 3.4 cm tumor, Ki-67 2.5%, IRS 12, respectively. One tumor had a variant not reported as pathogenic (p.Thr739Ala): male, 46 years old, 3.7 cm tumor, Ki-67 0.5%, IRS 0. USP8-wild-type silent corticotropinomas had IRS 0-2. Conclusion: One third of CD patients presented with somatic *USP8* mutation. Similar to another study, about 10% of silent corticotropinomas also presented somatic *USP8* mutation. Expression of SST5 was high in USP8-mutated CD and higher than wild-type group.

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Vitamin D Metabolism Alteration in Acromegaly and Its Impact on Calcium-Phosphorus Metabolism

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