Silent pituitary corticotroph tumors derive from the Tpit (aka TBX19) pituitary lineage. Accounting for ~ 30% of corticotroph tumors, they are not infrequently clinically aggressive and invade locally into adjacent sellar structures, making complete surgical resection challenging and contributing to their higher recurrence rates. How silent and active corticotroph tumor subtypes differ is not clear although some studies reported that silent corticotroph tumors exhibit reduced PC1 expression causing impaired POMC processing. We used single cell RNAseq to compare the transcriptome between silent (n = 2) and active (n = 4) corticotroph tumors at the single cell level. We obtained an average of 265 million reads, and 24,682 genes per patient with an average of 1,240 genes expressed and 3,5442 unique molecular identifiers (UMIs) detected per cell. We further defined 5 distinct cell populations from a total of 23,269 cells, namely tumor cells (62%), stromal cells (25%), immune cells (7%), progenitor cells (5%), and a minor population of erythrocytes (1%). Tumor cells clustered in an origin-dependent manner and all expressed POMC and TBX19. However, the gene signatures of silent and active corticotroph tumors differed in 3 major aspects. Firstly, and supporting prior studies, a series of hormone processing peptidase genes, including PC1 (aka PCSK1), PDIA3, SEC11C, SPCS1 and CTSB, were reduced in silent corticotroph tumors (p=5.54e-5) compared to active corticotroph tumors. Secondly, genes involved in organization of secretory vesicles such as SCG5, TIMP1, VGF, SYT17, LGALS3 and CALY were also reduced in silent corticotroph tumors, which could further compound their inability to secrete ACTH. Thirdly, the silent corticotroph tumors exhibited several features of endothelial-to-mesenchymal transition (EMT), including increased expression of the mesenchymal genes CDH2 (aka NCAD), COL1A1, PCDH9, FGF5, ID2 (p=8.4e-3), and loss of EPCAM, which regulate cell migration and movement. Upstream analysis suggested that aberrant STAT3 activation may be related to these changes. Consequently, we noted that the stromal content was higher in silent corticotroph tumors (47.5% vs. 18.13%), concordant with the observed EMT de-differentiation of tumor cells. In summary, our scRNAseq analysis provides an unprecedented precise investigation of the transcriptomic features of thousands of heterogenous corticotroph tumor cells simultaneously. We demonstrate that although silent corticotroph tumor cells still express the pituitary lineage markers PITX1 and TBX19, they exhibit EMT, potentially affording increased migratory capacity at the cost of reduced neuroendocrine function with inability to produce and secrete mature ACTH. Our findings provide novel insights into the pathogenesis of silent versus active corticotroph tumor, but may reveal novel molecular targets for treatment of these challenging tumors.

Neuroendocrinology and Pituitary
PITUITARY TUMORS

One Fourth of Adult Patients With Acromegaly Have Tall Stature With Similar Frequency in Males And Females

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Introduction: Tall stature (TS) is a manifestation of growth hormone (GH) excess, with higher prevalence reported for males. The aim of this study was (i) to evaluate the relationship between height of patients with GH excess related to midparental height (MPH) and population mean height; (ii) to test whether TS patients with acromegaly come from tall families. **Methods:** Single-centre, observational study on 101 consecutive adult patients with acromegaly and no family history of pituitary adenoma. Patients were analysed in two subgroups depending on height using country-specific data: 1) normal stature and 2) TS group, defined as either height above gender-specific 97 percentile or as >1.5 country-specific standard deviation (SD) from MPH. **Results:** Twenty-four percent of acromegaly patients (13 females/11 males) met one or both of the TS criteria. TS patients were significantly younger at the diagnosis (mean±SD, 33.6±13.4 vs 50.6±12.3 years) and at first symptoms (median 27.5, range 23-42 vs 41 (33-54) years) with greater tumour size and higher basal GH concentration than normal stature patients (p<0.01). The TS criteria based on the 1.5 SD above MPH identified more TS patients than the above 97 percentile height (92% vs 38%) and especially increased the diagnosis of TS in women (92% vs 31%). There was no difference in height of family members of acromegaly patients with or without TS. Height of family members were not taller than the population mean. **Conclusion:** One fourth of adult patients with acromegaly have TS with similar frequency in males and females. Based on our data TS patients with acromegaly do not come from tall families.

Neuroendocrinology and Pituitary
PITUITARY TUMORS

Prevalence of Abnormal Glucose Metabolism in Acromegaly & Impact of Treatment Modalities on Glucose Metabolism

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Objective: To determine the frequency of diabetes mellitus impaired glucose tolerance and impaired fasting glucose in Pakistani patients with acromegaly and to establish the impact of the intervention (surgery/ medical) on glucose metabolism.
Methods: Eighty-nine patients fulfilling the endocrine society criteria for acromegaly diagnosis were included.

A data of baseline, growth hormone (GH), Insulin-like growth factor-1 (IGF-1) level, Hemoglobin A1C (HbA1C), fasting blood glucose (FBG), and random blood glucose (RBS) levels were reviewed before and after the intervention (surgery/medical therapy). Normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes mellitus (DM) were defined based on the 2003 ADA criteria. Patients were grouped into normoglycemic (NGT) and dysglycemic (IFG, IGT, and DM) based on FBS, RBS, and HbA1C.

Results: Major risk factors for dysglycemia included age (15-45 years), male sex (33.70%), obesity (45.7%), and macroadenoma (76%). Both mean GH levels (58.29 vs. 54.36 ng/dl) and IGF-1 levels (862.98 vs. 824.32 ng/dl) were higher among the normoglycemic than dysglycemia. Pre-surgery, NGT, IFG, IGT, IFG, and IGT combined and DM were found in 48.31, 5.61, 1.1, 5.61, and 39.32 % of the subjects, respectively. Post-surgery, HbA1C improved in 79.5%, deteriorated in 6.8%, and remained the same in 13.6%. Similarly, it improved in 67.4.7% post-medical therapy. Both FBS and RBS improved post-surgery and medical therapy. Further, the number of anti-diabetic drugs used also decreased post-surgery.

Conclusion: Dysglycemia is more common among patients with acromegaly as compared to the general population and tends to be poorly controlled in untreated acromegaly. Glycemic control improves significantly after the surgery and medical therapy.

Keywords: Acromegaly, Diabetes Mellitus, Transsphenoidal surgery

Neuroendocrinology and Pituitary

PITUITARY TUMORS

Safety and Efficacy of Pegvisomant in Pediatric Growth Hormone Excess

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Objective: Pediatric growth hormone excess (GHE) and gigantism are mainly managed by pituitary surgery. However, a large percentage of patients require further medical management. Data for the pediatric population are scares and decisions are usually based on adult published data. We have initiated a study to investigate the efficacy and safety of pegvisomant in children and adolescents with GHE. MethodsThe study is registered in ClinicalTrials.gov (Identifier: NCT03882034, An open-label phase 3 study of the safety and efficacy of pegvisomant in children with growth hormone excess). Eligible patients must be children or adolescents (age: 24 months -18 years) with GHE with persistent disease after surgical or radiation therapy. The patients will receive pegvisomant via subcutaneous daily injection for one year and outcomes will be measured at baseline and at the end of the study. The main measure of efficacy is the change of IGF-1 from baseline to the end of the study. The main measure of safety is the description of side effects over the duration of the study. ConclusionsWe will collect data on the safety and efficacy of medical treatment for pediatric patients with GHE.

Neuroendocrinology and Pituitary

PITUITARY TUMORS

Somatotroph Adenomas have a Predilection to Invade the Cavernous Sinus and Resection of the Medial Wall of the Cavernous Sinus Offers the Highest Potential for Biochemical Remission in Acromegaly

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Recurrence and remission rates vary widely among different histological subtypes of pituitary adenoma. Invasion of the medial wall of the cavernous sinus is a known mechanism that may account for such failed clinical outcomes as its removal has long been considered unattainable. The use of modern endoscopic techniques allows for direct intraoperative evaluation of invasion and resection of the medial wall of the cavernous sinus with low morbidity when performed by highly experienced surgeons. In this retrospective study we evaluated 105 consecutive primary pituitary adenomas operated by a single surgeon including 28 corticotroph, 27 gonadotroph, 24 somatotroph, 15 lactotroph, 5 null-cell, 5 plurihormonal, and 1 dual adenoma; 53 caused hypersecretory syndromes, specifically acromegaly (30), hyperprolactinemia (15) and Cushing's disease (8). In each case, we performed meticulous intraoperative inspection of the medial wall with its surgical removal when invasion was suspected, regardless of functional status. Medial wall resection was performed in 46% of pituitary adenomas, and 38/48 walls confirmed pathologic evidence of invasion rendering a positive predictive value of intraoperative evaluation of medial wall invasion of 79%. Furthermore, we show for the first time that the rate of medial wall invasion among pathological subtypes is dramatically different. Somatotroph tumors invaded the medial wall much more often than other adenoma subtypes, 83% intraoperatively and 71% histologically, followed by plurihormonal tumors (40%) and gonadotrophs (33%), both with intraoperative positive predictive value of 100%. The least likely to invade were corticotroph, at a rate of 32% intraoperatively and 21% histologically, and null-cell adenomas at 0%. Removal of the medial wall caused no permanent morbidity with no carotid artery injuries and 2 patients with transient diplopia. We report that resecting the medial wall of the cavernous sinus in acromegaly offers the highest potential for biochemical remission with average postoperative day 1 GH levels at 0.96 ug/l and early surgical remission rates at 90% (100% with adjuvant therapy) based on normalization of IGF-1 levels 3 to 6 months after surgery; these results are significantly better than previously reported but longer follow-up is required for definitive conclusions. Our findings may explain the failed biochemical remission rates seen in acromegaly and illustrate the relevance of advanced surgical techniques for successful outcomes in pituitary surgery.