Title

New Transcriptional Insights into Silent and Active Corticotroph Pituitary Tumors at Single Cell Resolution

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and HDL-cholesterol levels. **Conclusion:** Increased serum hs-CRP levels in the GH-deficient patients with NFPTs suggested the contribution of GH deficiency to pathogenesis of inflammation associated with cardiovascular diseases.

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Low Risk for All-Cause Mortality Among Patients With Lung Neuroendocrine Tumors Co-Diagnosed With Pituitary Adenoma

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Context: Lung neoplasm often co-occur with pituitary adenoma (PA). However, whether co-diagnosis of lung neuroendocrine tumors (LNET) and PA constitute unique entity, and the impact of such co-diagnosis on patients outcome is yet to be defined. **Objective:** To compare the clinical characteristics of patients with LNET to those co-diagnosed with PA. **Design:** Retrospective, case-control study including patients diagnosed with LNET or PA between 2000 and 2016. **Setting:** The Surveillance, Epidemiology and End Results database. **Patients:** 2,947 patients had LNET, including 2,913 with LNET alone ("Sporadic") and 34 patients with both LNET and PA ("MENx"). **Main Outcome Measure(s):** All-cause mortality (ACM). **Results:** PA preceded LNET diagnosis in 85.3% of patients and had higher rates among LNET patients (34/2,947) than with any cancer (p<0.00001) and compared to patients with non-small cell lung cancer (NSCLC) (15/2,378, p=0.047). MENx patients were younger at diagnosis compared with NSCLC patients and PA (p=0.04). Among patients<60 years with LNET, co-diagnosis with PA was associated with lower ACM risk (Log-rank test, p=0.03). Adjusted ACM risk of patients with "MENx" was lower than sporadic LNET (hazard ratio 0.553, 95% confidence interval 0.309-0.99, p=0.046), especially among Caucasians, and a lower overall-mortality risk in patients <60 years with borderline statistical significance (p=0.071). **Conclusions:** Patients with both LNET and PA constitute a distinct morbidity and mortality profile compared with sporadic LNET possibly suggesting an undefined MEN syndrome. Additional studies to further investigate the natural course and genetic profile of patients with these neoplasms are needed.

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Markers of Aggressiveness in Craniopharyngiomas

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Craniopharyngiomas (CP) are rare tumors that may be locally aggressive. The presence of functional estrogen receptors (ER) has been reported in CP and might be related to risk of recurrence. Our aim is to ascertain if the expression estrogen and progesterone receptor (PR) might be associated with to recurrence in CP. Material and **Methods:** Descriptive retrospective observational study of patients with confirmed histology of CP and tissue sample available admitted to Virgen Del Rocio University Hospital (Seville, Spain) from January 1967 to October 2020 were included. Estrogen and progesterone receptor expression was analyzed by Immunohistochemistry. Ki-67 levels were also analyzed. Two CP groups were considereded according to Ki67 levels: Group A (Ki67<10%) and group B (Ki67>10%). As all variables followed a non-parametric distribution, U Mann Whitney, Chi-Square, and Z-test with Benjamini-Hochberg correction were used when needed. **Results:** Our study population includes 80 patients (46 male and 34 female), with a median age at diagnosis of 34 years [10-50.00]. Twenty-six patients were under 18 years old (children) with a median age of 7 years [4.5-10.00], and 54 were adults (aged 18 and above) with a median age of 45 years [33-58.50]. Our data shows higher recurrence rates when Ki67 levels staining were higher than 10%: 8/14 (57.2%) in comparison with Ki67<10% (6/14, 42.9%, p=0.018). In children we found 6 samples with Ki67<10% and 6 samples with Ki67 >10%; recurrences were observed in 2/6 (33,3%) in the first group and in 6/6 (100%) in the second, respectively (p= 0,199). In adults, we found 9 and 3 patients for high and low Ki67 levels, respectively. Recurrences were observed in 4/9 (44,4%) in the group A and in 2/3 (66,7%) in the group B, respectively (p= 0,28). There were no differences between age groups. In patients with positive ER, we observed an increased rate of recurrence: 12/23 (52.17%) versus 2/13 (15,38%) in patients with negative ER stain but it was no significant. (p=0,21). No association between PR and recurrence was observed. Conclusions: In our series, patients with CP with high Ki67 levels are more likely to recur. No clear association between ER, PR expression and recurrence was observed. These findings support the use of Ki67 as a marker of recurrence in CP. **Sources of Research Support:** Spanish Ministry of Health, ISCIII co-funded with Fondos FEDER (PI16/00175) and Novartis Oncology Spain.

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New Transcriptional Insights into Silent and Active Corticotroph Pituitary Tumors at Single Cell Resolution

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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.

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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.

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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.