Somatotroph pituitary neuroendocrine tumor

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A somatotroph pituitary neuroendocrine tumor (PitNET) is a type of tumor that originates from the somatotroph cells in the adenohypophysis.

Somatotroph pituitary neuroendocrine tumor, (GH producing adenomas, somatotropinomas) is an insidious disease with persistent hypersecretion of growth hormone and insulin-like growth factor 1, causing increased morbidity and mortality.

Epidemiology

The incidence of Somatotroph pituitary neuroendocrine tumors is estimated to be 2-3 cases per 100,000 people per year. They can occur at any age, but they are most common in adults between the ages of 30 and 50. The risk of developing is slightly higher in women than in men.

75 % are > 10 mm at the time of diagnosis.

Pathogenesis

Somatotroph adenoma pathogenesis.

Classification

Patients with acromegaly usually harbor macroadenomas measuring between 10 and 30 mm in maximal diameter. Giant (adenoma size ≥40 mm) GH-secreting pituitary tumors are rarely encountered.

see Giant somatotroph adenomas or invasive.

Co-secretion of growth hormone (GH) and prolactin (PRL) from a single pituitary neuroendocrine tumor is common. In fact, up to 25% of patients with acromegaly may have PRL co-secretion. The prevalence of acromegaly among patients with a newly diagnosed prolactinoma is unknown. Given the possibility of mixed GH and PRL co-secretion, the current recommendation is to obtain an insulin-like growth factor-1 (IGF-1) in patients with prolactinoma at the initial diagnosis. Long-term follow-up of IGF-1 is not routinely done [1)].

Clinical Features

Somatotroph adenoma clinical features.

Diagnosis

Somatotroph adenoma diagnosis.

Complications

They are typically recognized when they secrete GH excessively and cause the clinical syndrome of acromegaly. This recognition not only identifies a sellar mass as a somatotroph adenoma but also expands the therapeutic options. Occasional reports in the literature also describe ‘silent somatotroph adenomas,’ referring to adenomas that can be identified as somatotroph adenomas by positive immunohistochemical staining for GH, but are not associated with clinical evidence of GH excess. Some of these adenomas are totally silent, in that they are not associated with either clinical manifestations of GH excess or elevated serum concentrations of GH or IGF-1.

Treatment

Somatotroph pituitary neuroendocrine tumor treatment

Outcome

see Somatotroph adenoma outcome

Translational research studies

Sun et al. performed integrative analyses including bioinformatics analyses, functional studies, and clinical validation to investigate the pathological roles of SPHK1/S1P and evaluated the effectiveness of the S1P receptor 2 (S1PR2) inhibitor JTE-013 in GHPA treatment.

SPHK1/S1P signalling is abnormally expressed in patients with GHPA. Knockdown of SPHK1 suppresses S1P-mediated cell proliferation in GH3 Cells. Mechanistically, S1P inhibits apoptosis and autophagy while promoting the secretion of Growth Hormone (GH) by binding to the S1P receptor subtype 2 (S1PR2) in GH3 cells. Moreover, the function of S1PR2 in GH3 cells is mediated by the downstream Akt-Creb pathway. They then identify the S1PR2 as a novel target for therapeutic intervention in GHPA. Systemic administration of the potent and selective S1PR2 antagonist, JTE-013, significantly reduces both tumour size and GH secretion. Importantly, they identified preoperative serum S1P levels as a biomarker predicting poor prognosis in GHPA patients at follow-up.

The study shows that blocking SPHK1/S1P/S1PR2 axis can ameliorate the progression of GHPA, providing evidence of a promising therapeutic target for GHPA [2)].

Prospective observational studies

424 GHPA patients presenting to Beijing Tiantan Hospital, Capital Medical University between January 2015 and January 2023 was conducted. Spearman's correlation tests were performed to examine the relationship between IGF-1 and UA at baseline. Univariate and multivariate linear regression analysis was conducted to investigate the independent association between UA and IGF-1. Changes in postoperative IGF-1 and UA levels were followed prospectively, and the differences in UA levels between the biochemical remission and nonremission groups were compared.

At baseline, male patients, the lower the age, the higher the IGF-1 and body mass index (BMI), and the higher the UA levels. IGF-1 was significantly associated with UA after controlling for sex, age, and BMI ($r = 0.122$, $P = 0.012$). In adjusted multiple linear regression analysis, IGF-1 was independently associated with UA, and UA levels increased significantly with increasing IGF-1. During postoperative follow-up, UA decreased gradually as IGF-1 levels decreased. At 12 months postoperatively, UA levels were significantly lower in the biochemical remission group than in the nonremission group ($P = 0.038$).

In patients with GHPA, UA levels are associated with disease activity. Changes in UA levels should be taken into account in the comprehensive treatment of GHPA, patients presenting with HUA should be

given lifestyle guidance and appropriate urate-lowering treatment according to their condition to better improve their prognosis [3)]

Multicenter retrospective studies

Multicenter retrospective study of 604 patients with acromegaly submitted to pituitary surgery. Patients were classified into two groups according to serum PRL levels at diagnosis and immunohistochemistry (IHC) for PRL: a) GH&PRL-PAs when PRL levels were above the upper limit of normal and IHC for GH and PRL was positive or PRL levels were >100ng/and PRL IHC was not available (n=130) and b) GH-PAs who did not meet the previously mentioned criteria (n=474).

Results: GH&PRL-PAs represented 21.5% (n=130) of patients with acromegaly. The mean age at diagnosis was lower in GH&PRL-PAs than in GH-PAs (P<0.001). GH&PRL-PAs were more frequently macroadenomas (90.6% vs. 77.4%, P=0.001) and tended to be more invasive (33.6% vs. 24.7%, P=0.057) than GH-PAs. Furthermore, they had presurgical hypopituitarism more frequently (OR 2.8, 95% CI 1.83-4.38). IGF-1 upper limit of normality (ULN) levels at diagnosis were lower in patients with GH&PRL-PAs (median 2.4 [IQR 1.73-3.29] vs. 2.7 [IQR 1.91-3.67], P=0.023). There were no differences in the immediate (41.1% vs 43.3%, P=0.659) or long-term post-surgical acromegaly biochemical cure rate (53.5% vs. 53.1%, P=0.936) between groups. However, there was a higher incidence of permanent arginine-vasopressin deficiency (AVP-D) (7.3% vs. 2.4%, P=0.011) in GH&PRL-PAs patients.

Conclusions: GH&PRL-PAs are responsible for 20% of acromegaly cases. These tumors are more invasive, larger and cause hypopituitarism more frequently than GH-PAs and are diagnosed at an earlier age. The biochemical cure rate is similar between both groups, but patients with GH&PRL-PAs tend to develop permanent postsurgical AVP-D more frequently [4)]

Retrospective cohort studies

Sixty-seven acromegalic patients with giant GHPAs and 67 patients with macro GHPAs (10-39 mm), matched for age and gender from the same hospital during the same period, were retrospectively recruited. The clinical characteristics, treatment, and outcomes were analyzed.

Enlargement of the extremities and facial features were the most common symptoms in most patients (92.5%). Compared with the macroadenoma group, more frequent visual impairment (86.6% vs. 25.4%, P < 0.001) and gonadal axis dysfunction (49.3% vs. 34.3%, P = 0.008), higher preoperative fasting GH, nadir GH after OGTT and IGF-1 levels, and a higher proportion of extrasellar tumor invasion were seen in the giant adenoma group. As the adenoma size increases, the total resection rate decreases, and postoperative complications and multimodal treatment strategies increase significantly. Fasting and nadir GH levels remained higher at 1 week postoperatively, and there were more surgical complications and cases of anterior hypopituitarism in the giant group. After a median follow-up of 36 months, 12 patients (36.4%) in the giant GHPA group and 17 (36.2%) in the macro GHPA group achieved biochemical remission. Other factors such as age of onset, age of diagnosis, delayed diagnosis time, metabolic complications, p53 positive rate, and Ki-67 index showed no significant difference between the two groups.

With aggressive multimodal therapy, the biochemical remission rate of acromegalic patients with giant GHPAs is comparable to that of patients with macroadenoma. However, postoperative complications and hypopituitarism need to be closely monitored [5].

Cross-sectional observational studies

Saliva samples from 42 patients and 20 healthy individuals were selected for third-generation sequencing. The PA group included four clinical phenotypes: adrenocorticotropic hormone-secreting PA (n = 6), growth hormone-secreting PA (n = 9), prolactin-secreting PA (n = 18), and nonfunctioning PA (n = 9). All samples were sequenced, and the data were clustered and de-chimerized to obtain information regarding the abundance of operational taxonomic units. We found that the species distributions in the saliva of PA patients were more abundant than those of healthy individuals. A total of 82 genera were identified across all samples, of which 14 and 17 genera were more abundant in the saliva samples of patients with PA and healthy individuals, respectively. In the phenotypic functional prediction, the phenotypes of anaerobic and Gram-positive organisms were more commonly seen in patients with PA than in healthy individuals. The bioinformatics prediction indicated that multiple metabolic pathways were involved in the pathogenesis of PA. In conclusion, this study highlighted the associations of salivary microbiome profiles with PA, which may improve the existing understanding of the pathogenesis of PA and provide diagnostic and therapeutic targets for PA.IMPORTANCEThe gut and salivary microbiomes have been widely reported to be significantly associated with a number of neurological disorders. The stability of the microbiome in the oral cavity makes it a potentially ideal sample that can be conveniently obtained for the investigation of microbiome-based pathogenesis in diseases. In the present study, we used a single-molecule long-read sequencing technique to study the distribution of the salivary microbiota in patients with pituitary adenoma (PA) and healthy individuals, as well as among four clinical phenotypes of PA. We found that the diversity of salivary microbes was more abundant in PA patients than in healthy individuals. We also observed some unique genera in different PA phenotypes. The bioinformatics-based functional predictions identified potential links between microbes and different clinical phenotypes of PA. This study improves the existing understanding of the pathogenesis of PA and may provide diagnostic and therapeutic targets for PA [6]

Case series

Somatotroph adenoma case series.

Case reports

Somatotroph adenoma case reports.

1)
Manuylova E, Calvi LM, Hastings C, Vates GE, Johnson MD, Cave WT Jr, Shafiq I. Late presentation of acromegaly in medically controlled prolactinoma patients. Endocrinol Diabetes Metab Case Rep. 2016;2016. pii: 16-0069. PubMed PMID: 27855229.
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6)

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