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Utility of Pre-Operative ACTH Stimulation Testing to Differentiate Silent Corticotroph Adenomas from other Non-Functional Pituitary Macroadenomas: A Brief Report

Buehler L[1], Polanco Santos C[1], Choudhary C[2], Mishra K[3], Sinha V[4], Bena J[5], Hamrahian AH[6], Kennedy L[1], Pantalone KM[1*]

[1]Cleveland Clinic Department of Endocrinology & Metabolism, 9500 Euclid Ave, Cleveland, OH 44195, Desk F20
[2]Bayhealth Medical Center, 640 S State St, Dover, DE 19901
[3]Henry Ford Medical Group, 2799 W Grand Blvd, Detroit, MI, 48202
[4]Mercy Health Toledo, 3841 Navarre Avenue, Oregon, OH 43616
[5]Cleveland Clinic departments of Quantitative Health sciences, 9500 Euclid Ave, Cleveland, OH 44195
[6]Johns Hopkins Comprehensive Adrenal Center, 601 N. Caroline St, Baltimore, MD 21287

[*]***Corresponding author:*** *Kevin M. Pantalone, DO, ECNU, FACE, 9500 Euclid Avenue, Desk F-20, Cleveland, Ohio, 44195. Tel: 330-888-4000.*

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Abstract

Purpose: *To assess if adrenocorticotrophic hormone (ACTH) stimulation testing performed during preoperative evaluation of nonfunctional pituitary macroadenoma can aid in identification of ACTH staining pathology.*

Methods: *A retrospective chart review was conducted on 148 patients with histopathologically confirmed pituitary macroadenoma who underwent a preoperative ACTH stimulation test. Of those, 14 (9.5%) showed diffuse ACTH staining, 75 (50.6%) showed other-staining (pituitary hormones other than ACTH), and 59 (39.9%) were non-staining. Delta total cortisol levels (μg/dL) at 30 and 60 minutes from baseline were calculated. The basal and maximal delta cortisol (mean+/-SD) were compared between the ACTH staining pituitary macroadenoma and the non-ACTH staining, other-staining, and non-staining tumors individually using two-sample t-tests.*

Results: *The mean basal cortisol level in the ACTH staining group (13.9 ± 4.2) was higher vs. the non-ACTH staining (10.6 ± 4.8, P=0.012), other-staining (10.7 ± 4.9, P=0.018) and the non-staining (10.5 ± 4.6, P=0.012) tumors.*

The maximal delta cortisol in the ACTH staining group (17.3 ± 8.6) was not statistically different, vs. the non-ACTH staining (16.3 ± 5.8, P=0.67), other-staining (15.6 ± 5.5, P=0.47) or non-staining (17.3 ± 6.1, P=0.97) tumors.

The mean basal and maximal delta cortisol levels in the other-staining group were not statistically different compared to the non-staining group (P=0.77 and P=0.10, respectively).

Conclusion: *In our study, basal cortisol levels were higher in patients with ACTH-staining pituitary macroadenoma. A multicenter study, affording a larger number of ACTH-staining tumors, may determine if the ACTH-stimulation test can be useful in preoperatively identifying ACTH-staining pathology.*

Keywords: *Adrenocorticotropic hormone, cortisol, pituitary adenoma, adrenal insufficiency.*

Introduction

Silent corticotroph adenomas (SCAs) are pituitary tumors that stain positive for adrenocortocotrophic hormone (ACTH) but are clinically and biochemically silent. SCAs are estimated to make up about six percent of all non-functioning adenomas (NFAs) and about twenty percent of all pituitary adenomas that stain positive for ACTH [1,2]. Given their clinically silent nature, SCAs typically present with mass effect or panhypopituitarism and are diagnosed retroactively on pathology in the postoperative period. Prior literature has shown that the postoperative course of silent ACTH-staining adenomas differs from that of other NFAs [1,3]. Some studies suggest that SCAs may be associated with a higher rate of adrenal insufficiency (AI) and panhypopituitarism after resection [4-6]. They have also been shown to confer a higher risk of cavernous sinus invasion and tumor recurrence [1,7,8]. Given the elevated risk for postoperative complications in patients with SCAs, preoperative recognition could be useful to help guide management and monitoring in the early postoperative period.

ACTH stimulation testing is a routine part of the preoperative evaluation for macroadenomas. This is done to rule out adrenal insufficiency prior to surgery in patients that do not present with overt Cushing's syndrome. Prior studies suggest that preoperative dynamic testing of the hypothalamic-pituitary-adrenal (HPA) axis may be impaired in SCAs despite their hormonally silent nature [1]. In this study, we aim to determine if routine preoperative ACTH stimulation testing can be used as a tool to differentiate SCAs from other NFAs prior to surgery to help guide perioperative management.

Methods

A retrospective chart review was conducted on 148 patients with histopathologically confirmed pituitary macroadenomas who underwent preoperative ACTH stimulation testing at our institution. Patients were excluded if they had known adrenal insufficiency prior to surgery, had ACTH stimulation testing at an outside institution, were on any form of glucocorticoids, had a serum albumin < 2.5 mg/dL, or were taking oral contraceptives. Patients with rare or focal staining, as well as patients that had overt Cushing's syndrome (identified through overnight dexamethasone suppression test, 24-hour urine free cortisol, and/or late night salivary cortisol testing) were excluded. From 148 patients, 14 (9.5%) showed diffuse ACTH staining, 75 (50.6%) showed other-staining (diffuse staining for anterior pituitary hormones other than ACTH), and 59 (39.9%) were non-staining (no staining for any anterior pituitary hormones). Preoperative ACTH stimulation tests were reviewed and the delta total cortisol levels (μg/dL) at 30 and 60 minutes from baseline were calculated.

Normality was evaluated using a histogram and the Shapiro Wilk test. The basal and maximal delta cortisol (mean +/- standard deviation) were compared between the ACTH staining pituitary macroadenoma and the non-ACTH staining (n=134), other-staining (n=75) and non-staining (n=59) tumors individually using two-sample t-tests and were presented as means and standard deviations (Figure 1).

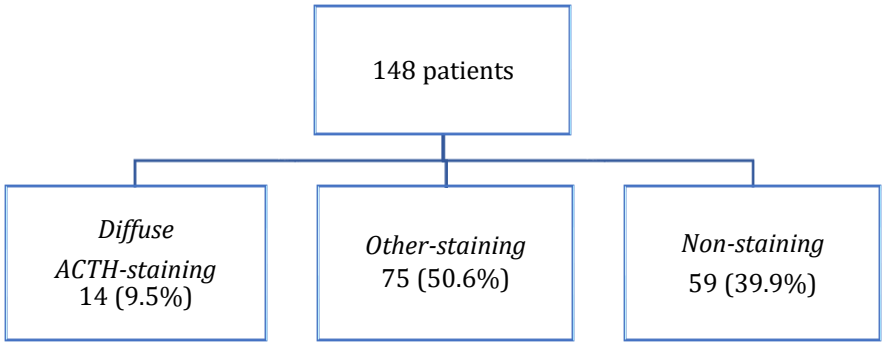

Figure 1: Categories of staining on pathology.

Results

The mean basal cortisol level in the ACTH staining group (13.9 ± 4.2 μg/dL) was higher vs. non-ACTH staining (10.6 ± 4.8 µg/dL, P=0.012), other-staining (10.7 ± 4.9 µg/dL, P=0.018) and the non-staining (10.5 ± 4.6 µg/dL, P=0.012) tumors (Tables 1-3).

Table 1: Cortisol Change Comparisons of ACTH-Staining Vs. All Others

	TOTAL (n= 148)	ACTH-STAINING (n= 14)	ALL OTHERS* (N= 134)	p-VALUE
Basal Cortisol(µg/dL)	10.9±4.8	13.9±4.2	10.6±4.8	0.012
Maximum Cortisol Change(µg/dL)	16.4±6.1	17.3±8.6	16.3±5.8	0.67

* ALL OTHERS: Other-staining + Non-staining

Table 2: Cortisol Change Comparisons of ACTH Staining Vs. Non-Staining

	ACTH-STAINING (n= 14)	NON-STAINING (n= 59)	p-VALUE
Basal Cortisol(µg/dL)	13.9±4.2	10.5±4.6	0.012
Maximum Cortisol Change(µg/dL)	17.3±8.6	17.3±6.1	0.97

Table 3: Cortisol Change Comparisons of ACTH-Staining Vs. Other Staining

	ACTH-STAINING (n= 14)	OTHER- STAINING (n= 75)	P-VALUE
Basal Cortisol(µg/dL)	13.9±4.2	10.7±4.9	0.018
Maximum Cortisol Change(µg/dL)	17.3±8.6	15.6±5.5	0.47

The maximal delta cortisol in the ACTH staining group (17.3 ± 8.6 µg/dLg/dL) was not statistically significantly different, vs. the non-ACTH staining (16.3 ± 5.8 µg/dL, P=0.67), other-staining (15.6 ± 5.5 µg/dL, P=0.47) or non-staining (17.3 ± 6.1 µg/dLg/dL, P=0.97) tumors (Tables 1-3). The mean basal and maximal delta cortisol levels in the other-staining group were not statistically different compared to the non-staining group (P =0.77 and P=0.10, respectively).

Discussion

The aim of this study was to determine if ACTH stimulation testing can be used to help recognize silent ACTH-producing macroadenomas prior to surgical resection. This is clinically important because SCAs have been associated with a higher likelihood of adrenal insufficiency and other complications after surgery despite being hormonally silent in nature [4-6]. Early recognition of SCAs would allow clinicians to approach these patients with a higher degree of monitoring and treatment for complications, particularly AI, in the early postoperative course. Preoperative dynamic testing might also potentially help to identify patients with subclinical or cyclic Cushing's disease that may have been missed during the pre-operative evaluation.

Several previously published studies have investigated the importance of differentiating SCAs from other NFAs before undergoing surgery. Some prior research has shown that silent ACTH-staining tumors have significantly higher rates of adrenal insufficiency after surgery even with normal preoperative serum cortisol and ACTH levels [5,6]. Other studies have shown patients with these types of silent tumors have an increased risk for impairment of other pituitary hormonal axes as well, especially hypothyroidism [1,4]. These data suggest that patients with SCAs could benefit from closer perioperative monitoring of the HPA and other pituitary axes to prevent hormonal insufficiencies after surgery. This might also suggest a benefit from potential use of preemptive treatment with glucocorticoids in SCA patients given their higher risk for AI postoperatively.

Our study's results showed significantly higher basal cortisol levels in ACTH-staining versus other types of NFAs (non-staining and other-staining). We also showed significantly higher levels of basal cortisol when comparing non-staining and other-staining in individual comparisons. However, there was no statistically significant difference in the delta cortisol change at 30 and 60 minutes when comparing ACTH-staining to the other groups. While basal cortisol levels in the ACTH-staining group were significantly higher vs. the other-staining and non-staining groups, the large variability in values does not allow clinical utility.

It has been hypothesized that SCAs have a higher risk for postoperative AI due to local secretion of ACTH by tumor cells that may suppress the surrounding normal corticotroph cells resulting in impaired ACTH production as they recover functionality after surgery [1]. Other authors have suggested that postoperative AI in this population could be due to mislabeling of certain SCA patients who may have actually had subclinical Cushing's (SCC) or cyclical Cushing's disease (CCS) [1]. Some of these cases of SCC or CCS could perhaps be identified by a robust cortisol response (delta cortisol) to Cosyntropin injection, during the pre-op pituitary function testing. Our data did not observe any difference in delta cortisol response during the Cosyntropin stimulation tests conducted in our patients with ACTH- staining vs. non-ACTH-staining pathology, but the sample size was small and the delta cortisol response among our patients was rather heterogeneous.

In congruence with our study's findings, previous research has shown that SCAs are associated with higher baseline plasma cortisol levels prior to surgery. A study by Guttenberg et al. showed that 40% of patients with SCAs had elevated plasma cortisol or 24-hour urine free cortisol (UFC) levels prior to surgery [9]. Other research has shown that SCAs were associated with elevated preoperative ACTH but with normal cortisol levels [1,9]. However, there have been several other studies published that did not show difference in preoperative ACTH or cortisol levels in these patients before resection [4,10]. Prior literature has suggested that the discrepancy in preoperative elevated cortisol and/or ACTH levels with apparent lack of functionality SCA patients may be due to impaired conversion of pro-opiomelanocortin (POMC) to ACTH resulting in a biochemically inactive compound [7].

Our study had several limitations that are important to note. First, this study was retrospective in nature, and is therefore inherently vulnerable to bias. Furthermore, our study was limited by the small sample size of ACTH-staining macroadenoma group, as well as by the larger variability in the delta cortisol response among the ACTH-staining group compared with other groups. This may have contributed to the fact that our study observed no differences in the maximal delta cortisol level among groups.

Despite the aforementioned limitations, our results did show significantly higher basal cortisol levels in patients with ACTH-staining pituitary macroadenoma. A multicenter study, affording a larger number of ACTH-staining tumors, would be appropriate to further evaluate if the ACTH-stimulation test can be useful in pre-operatively identifying ACTH-staining pathology. This information would help guide perioperative management of SCAs and could potentially help to identify patients with SCC or CCS during the pre-operative evaluation.

Conflicts of interest: The authors report no conflicts of interest as it pertains to the subject matter of this manuscript.

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Ethical Compliance: This study was approved by the Cleveland Clinic Institutional Review Board. A waiver of informed consent was obtained. Ethical approval was granted by the Cleveland Clinic Institutional Review Board.

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