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The Expression of Glucocorticoid Receptor in Patients with Small Cell Lung Cancer with or Without Ectopic Adrenocorticotropic Hormone Syndrome

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Abstract

Purpose: Ectopic Adrenocorticotropic Hormone (ACTH)-secreting syndrome (EAS) is a relatively rare disease. EAS could not be inhibited by endogenous or exogenous glucocorticoid, which may be its most important characteristic. We guess the difference of Glucocorticoid Receptor (GR) expression maybe the reason of no response to exogenous glucocorticoid in EAS. Therefore, we aimed to explore the difference in the expression of GR in Small Cell Lung Cancer (SCLC) with or without EAS.

Methods: In this study, we first report one patient with EAS caused by SCLC, and we examined ACTH and GR expression of pulmonary tissue as positive control, and then we examined the ACTH and GR expression in SCLC patients with or without EAS.

Result: Immunochemistry analysis showed that there is no obvious difference in the expression of GR in SCLC without EAS compared with normal people. While in the EAS patient, GR expression was absent in the tissue.

Conclusion: Therefore, our study revealed the difference of GR expression in Small Cell Lung Cancer (SCLC) with or without EAS.

Keywords: Small cell lung cancer; Ectopic ACTH syndrome; Glucocorticoid receptor

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Introduction

Ectopic Adrenocorticotropic Hormone (ACTH)-secreting syndrome (EAS) is a relatively rare disease with an incidence of one per million per year [1]. EAS is reported to be associated with many malignant tumors [2]. During recent years, several tumors such as Small Cell Lung Carcinoma (SCLC), neuroendocrine tumors, phaeochromocytomas, medullary carcinoma of the thyroid have emerged as causes of EAS [3,4], while the major source is eventually demonstrated in the lung. Clinically, the presentation of EAS is similar to Cushing Disease (CD) and poses a diagnostic challenge in localization of the ACTH source. The manifestations of EAS include hypertension, edema, hypokalemia, weakness and abnormal glucose tolerance and so on. Biochemical testing showed obviously increased plasma ACTH and cortisol level, which could not be inhibited by endogenous or exogenous glucocorticoid [5].

Glucocorticoids, a class of stress-induced steroid hormones synthesized by adrenal cortex, which is strictly under the control of the hypothalamic-pituitary-adrenal axis [6]. Glucocorticoids in humans are known to regulate diverse cellular functions including development, homeostasis, metabolism, cognition and inflammation. Endogenous glucocorticoid levels in the serum display a classic circadian pattern, peaking at the beginning of the period of highest activity. High level of ectopic serum ACTH cannot be suppressed by endogenous or exogenous glucocorticoid, and this is the cardinal characteristic of ectopic ACTH syndrome (EAS).

Glucocorticoids mediate their effect through intracellular GR, which belongs to a large family of transcription factors known as the nuclear hormone receptors. It is well documented that the level of GR protein determines the magnitude of glucocorticoid response. Therefore, we guess the difference in the expression of GR may play an important role in EAS. Previous studies in SCLC cell line showed decreased or absent expression of Glucocorticoid Receptor (GR) [7,8]. While the

Table 1: Biochemical characteristics of the patient.

Variable Blood tests	Test Value	Reference range
Hemoglobin (g/L)	125	110-150
White cell count (×10^9)	8.99	4-10
Platelet count (×10^9)	116	100-300
Blood glucose (mmol/L)	20.37	3.9-6.1
Potassium (mmol/L)	2.61	3.5-5.3
Calcium (mmol/L) Phosphate (mmol/L) AST (U/L) ALT (U/L) TG (mmol/L) CHO (mmol/L)	1.83 0.63 62 24 1.19 5.35	2.11-2.52 0.85-1.51 0-40 0-35 0.7-1.7 3.11-5.17
Creatinine (mg/dL)	53	41-81
Serum ACTH (pg/mL) 0AM 8AM 4PM Serum cortisol (ug/dl) 0AM 8AM 4PM	 328.79 384.08 288.35 64.38 70.88 68.52	
24-hour urinary free cortisol (ug/24h) 24-hour urinary potassium (mmol/24h)	4101.90 97.53	50-403 25-100
TSH (uIU/mL)	0.21	0.27-4.2
Free thyroxine (pmol/L) PTH (pg/mL) Calcitonin	 108.8 6.42	 15-65 0-5.0

evidence is still relatively weak. Therefore, we aimed to compare the ACTH and GR expression in SCLC patients with or without EAS.

Methods and Materials

Immunochemistry

The study was approved by Ethics Committee of Beijing Luhe Hospital. We collected pulmonary tissue from healthy, non-EAS-SCLC, EAS-SCLC patients. Meanwhile, we collected tissue from pituitarium as positive control. The expression of GR and ACTH were examined by immunochemistry.

Results

The case and laboratory examinations

A 70-year-old female visited her primary care for worsening fatigue with lower limbs for more than 20 days. The patient has a history of more than 60 years of heavy smoking, 10 cigarettes per day. Laboratory testing as an outpatient revealed hypokalemia of 2.15 mmol/l (3.5 to 5.5 mmol/l). In addition, the patient showed increased blood pressure, blood glucose level and hypoproteinemia. There was no history of diabetes mellitus or hypertension. The patient was then admitted to the hospital. The vitals were heart rate of 74 bpm, blood pressure of 144/66 mmHg, and respiratory rate of 18 bpm. Physical exam showed edema in the lower limbs, the rest of exam was within normal limits.

After admission, her hypokalemia was refractory although continuous oral and intravenous potassium supplements. The 24-h urine potassium was high (97.53 mmol/L), suggesting renal loss. Serum ACTH level of 0 am-8 am-4 pm were 328.79, 384.08 and 288.35 pg/mL respectively. Serum cortisol level of 0 am-8 am-4 pm were 64.38, 70.88 and 68.52 ug/dl respectively. The 24-h urine free cortisol level was 4101.9 ug. Recumbent test: renin-AII-ALD: 13.17-171.24-119.14 pg/mL; standing test: renin-AII-ALD: 12.82-165.04-105.16 pg/mL. No obvious abnormality was observed in pituitary MRI plain scan. Parathyroid ultrasonography showed low echo nodule in right parathyroid subgroup. Thyroid ultrasonography showed multiple nodules in thyroid. Subsequent contrast enhanced CT scan of the lung showed multiple enlarged lymph nodes in mediastinal and right lung portal areas. Density nodules of soft tissue under the pleural membrane of the lower right lung, pulmonary interstitial fibrosis, complicated with pulmonary infection, bilateral pleural hypertrophy, arteriosclerosis. Neither low-dose or high-dose dexamethasone test showed no inhibition of cortisol (>63.44 ug/dl). The metabolic findings, high ACTH level with radiologic and histological evidence, made ectopic ACTH syndrome from small cell lung cancer the most likely diagnosis. Primary laboratory results of the patient are summarized in Table 1.

ACTH and GR Expression in SCLC Patients with or Without EAS

High-dose dexamethasone suppression test is well known to be an important test in the diagnosis of ectopic ACTH syndrome. We examined the ACTH and GR expression in SCLC patients with or without EAS. The pituitary gland tissue was also stained with ACTH and GR antibodies as positive control. There was no difference in the ACTH and GR expression between control and SCLC patients without EAS (Figure 1). Compared with control, ACTH expression obviously increased while GR expression reduced in the SCLC patient with EAS (Figure 2), suggesting the reduction of GR expression may contribute to the no inhibition of high-dose dexamethasone.

Discussion

The anti-inflammatory and immunosuppressive effects of glucocorticoids are exploited extensively for the treatment of many inflammatory conditions. Endogenous glucocorticoids are stress-induced hormones synthesized under the control of the hypothalamic-pituitary-adrenal axis. High level of glucocorticoid

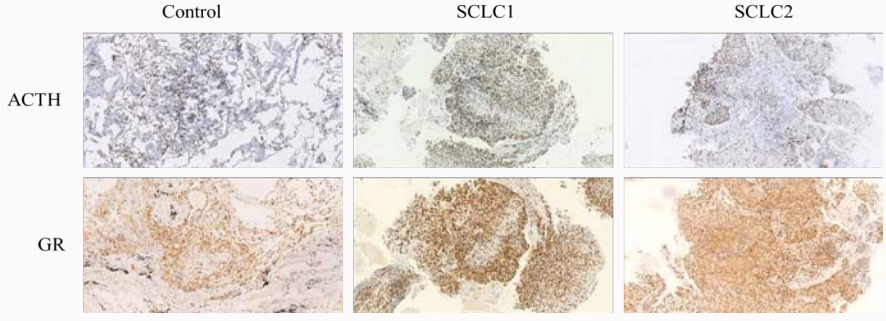

Figure 1: ACTH and GR expression of pulmonary tissue in control and two non-EAS-SCLC patients.

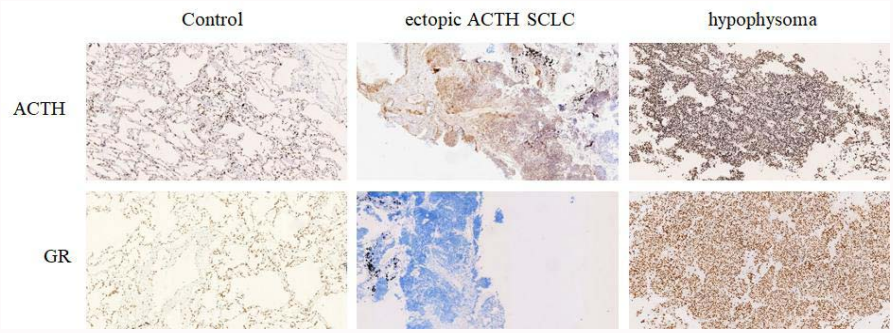

Figure 2: ACTH and GR expression in pulmonary tissue in the EAS-SCLC patient. Pituitarium tissue was as a positive control.

could inhibit the secretion of ACTH, which is named as feedback. While the regulation is out of control in EAS. High-dose dexamethasone suppression test has been applied in the diagnosis of EAS based on the characteristic. However, the underlying mechanism is not clear. Multiple mechanisms have been proposed to explain the phenomenon. Reduced GR expression is thought to be an important factor in mediating glucocorticoid resistance.

The GR is a ubiquitously expressed protein, found in almost all human cell types and tissues at appreciable levels. It is well-established that the level of GR expression is closely correlated with the magnitude of the glucocorticoid response [9]. Therefore, GR expression level may be an important determinant of the glucocorticoid response [10]. Several studies have shown that reduced GR expression in primary acute lymphoblastic leukemia cells is associated with initial resistance to glucocorticoid therapy, relapse, and poor prognosis [11,12]. In such cell lines including SLC cell lines, reduced GR expression was reported [10,13]. In our study, we collected pulmonary tissue from healthy, SCLC patients with or without EAS. Meanwhile, we collected tissue from pituitarium as a positive control. Immunochemistry analysis showed that there is no obvious difference in the expression of GR in SCLC patients without EAS compared with control group. While in SCLC patients with EAS, no obvious GR expression was seen in the pulmonary tissue. The results indicate that reduced GR expression may explain the no response to high-dose dexamethasone suppression test.

Several studies explored the mechanism of GR downregulation in cell lines. It is reported that glucocorticoid-induced downregulation of GR mRNA has been attributed to reduce transcription of the GR gene as well as decreased stability of the GR mRNA [7,8]. While no data available of GR expression of pulmonary tissue in the SCLC patient with EAS. Suggesting the reduction of GR expression may contribute to the no inhibition of high-dose dexamethasone. More samples are still needed to confirm the phenomenon and further studies are needed to illuminate the mechanism of GR downregulation or absent.

Conclusion

In SCLC patients with EAS, the reduction of GR expression may contribute to the no inhibition of high-dose dexamethasone.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by Ethics Committee of Beijing Luhe Hospital. This article does not contain any studies with animals performed by any of the authors.

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