SERUM ACTH LEVELS IN PATIENTS WITH POLYCYSTIC OVARIAN DISEASE

G. OHEL (*) - M. KATZ (**) - C. TOBLER - R. MILLAR
(*) Present address: Department of Obstetrics and Gynecology, Hadassah University Hospital - Jerusalem (Israel)
(**) Department of Obstetrics and Gynaecology, School of Medicine, University College - London

Summary: Serum adrenocorticotrophic hormone levels were assayed in 8 patients with polycystic ovaries and a similar number of control subjects. Serum ACTH concentrations were normal in 6 patients and marginally elevated in 1. Investigations of markedly elevated readings in another patient showed this to be due to an interfering factor rather than the ACTH molecule itself.

INTRODUCTION

Polycystic ovarian disease (PCO) is associated with disturbances of the hypothalamic-pituitary-ovarian axis. Disturbance of the hypothalamic-pituitary component is manifested by inappropriate gonadotrophin secretiton (Yen Chaney and Judd, 1976) in the majority of patients and by elevated prolactin levels in some patients (Duignan, 1976). Plasma levels of growth hormone, TSH and ACTH secretions have not been carefully investigated. There is a considerable body of evidence to suggest that adrenocortical overactivity contributes to the circulating pool of androgens which are commonly elevated in this condition (Leventhal and Scommegna, 1963; Mahesh and Greenblatt, 1964; Gabrilove, Sharma and Dorfman, 1965; Givens, Anderson and Ragland, 1975; Lachelin, Barnett and Hopper, 1979). The ability of corticosteroids to induce ovulation (Smith, Steinberger and Perloff, 1965) and the effectiveness of dexamethasone in suppressing plasma androgens (Duignan, 1976; Kirschner and Jacobs, 1971) in patients with this condition provides further circumstantial evidence, that, in PCO, adrenocortical hyperfunction might be due at least in part to a suppressible factor of anterior pituitary origin. Thus it is surprising that ACTH secretion has not been well documented in PCO. The present study was undertaken to determine ACTH concentration in this syndrome.

PATIENTS AND METHODS

Eight hospitalized patients, aged 22-31 years, with PCO confirmed by laparoscopy or laparotomy, were studied. As controls, eight age-matched regularly menstruating women, who were admitted to the gynaecological wards for nonendocrine conditions, were studied during the early follicular phase of their menstrual cycle. Three venous blood samples were collected through a No. 19 butterfly at 0, 30 and 40 minutes, the first sample being taken between 08.00 h and 10.00 h. Blood collected into precooled tubes, was immediately separated and then stored at −20 °C until assay. Plasma luteinizing hormone (LH), testosterone (T), androstenedione (A) and dehydroepiandrosterone sulphate (DHEAS) were estimated in the 0 minute sample. Plasma ACTH and cortisol (F) concentrations were measured in all 30 and 40 minute samples. A 24-hour urine was collected prior to the day of blood sampling and urinary 17-oxo (17-OS) and oxogenic (17-OGS) steroids were assayed. Informed consent was obtained from all subjects.

ASSAYS

Plasma ACTH was determined by radioimmunoassay (Berson and Yalow, 1968) using the CIS kit (Serono Laboratories). The sensitivity of the assay was 11 pg/ml. Intra- and Interassay coefficient of variation was 16% +

26% respectively. Cross reactivity with naturally occurring peptides, ACTH related peptides (αMSH, βMSH, βLPH, γLPH, β endorphin) and fragments of ACTH 11-24, 1-10, 25-30 was less than 1.5%. Fragment 1-16 of ACTH cross-reacted 3%. In our hands mean plasma ACTH in 10 normal subjects was 41 pg/ml with a range of 10-69 pg/ml (cf. manufacturer mean 38.1 pg/ml and a range of 10-100 pg/ml for normal subjects.) In samples from subjects presenting at endocrine clinics who exhibited suppression of plasma cortisol with 0.5 mg dexamethasone q.i.d. plasma ACTH was also suppressed. Patients exhibiting increased cortisol in response to the insulinstress test also showed a concomitant elevation of plasma ACTH.

Cortisol was measured using a previously described radioimmunoassay technique (Carr, Millar and Crowley, 1977). Plasma T (Millar and Kewley, 1975) ,A (as described in Katz, Cohen and Carr, 1979), DHEAS (Buster and Abraham, 1972) and LH (Midgley Jr., 1966) were measured conventional radioimmunoassay. Urinary 17-OS and 17-OGS were estimated by the methods described by Drekter (1952) and Few (1961), respectively. All samples were assayed in the same batch.

RESULTS

Plasma ACTH concentrations are shown in fig. 1. In the control subjects plasma ACTH values were less than 38 pg/ml and five of eight subjects had one or both readings at the sensitivity of the assay. Six of eight patients with PCO had normal ACTH concentrations with four having one or both values at the sensitivity of the assay. One patient (case no. 6) had levels marginally above the range of the control subjects, but within the normal range for our laboratory, previously determined in 10 normal subjects (10-69 pg/ml). However, in another patient (case no. 2) readings for ACTH were considerably elevated. Plasma F concentrations were similar in PCO patients and in controls.

There were no obvious correlations between LH, T, A, DHEAS, Cortisol or

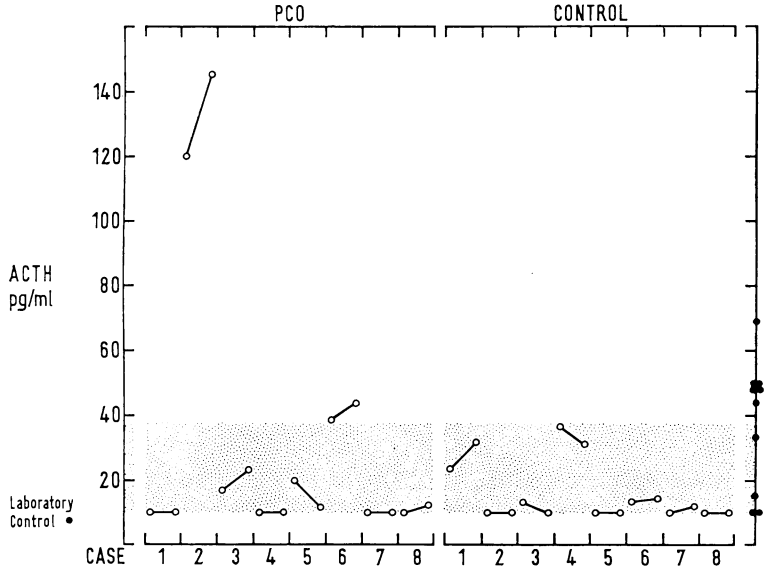

Fig. 1. — Plasma ACTH in 8 patients with PCO, 8 control subjects (hatched bar represents control range) and 10 subjects previously tested to assess the normal range for our laboratory.

Table 1. — *Dexamethasone (DMZ) Suppression - Case no. 2.*

	ACTH (pg/ml)		Cortisol (nmol/l)		DHEAS (μmol/l)
	A	B	A	B	
Baseline 1	140 *	165 *	473	648	8.7
Baseline 2 Pre - DMZ	230	250	490	469	11.9
After DMZ - 1 mg	240	250	<70	<70	6.6
After DMZ - 2 mg daily	200	180	<70	<70	1.8

* Previous assay of same samples gave ACTH values of (A) 120 and (B) 145 pg/ml.

Urinary Steroids and ACTH concentrations, but the number studied was small.

Case no. 2 was a 22 year old female with severe oligomenorrhea. She had no clinical evidence of hyperandrogenism or of adrenocortical over-activity. At laparoscopy she was found to have large bilateral polycystic ovaries.

Basal plasma ACTH values were 120 pg/ml and 145 pg/ml in two consecutive plasma samples taken 10 minutes apart. Plasma LH, A, T, DHEAS and urinary 17-OS were elevated, but plasma F and urinary 17-OGS were within normal limits. Two weeks after the initial ACTH assay, a dexamethasone suppression test was performed, the results of which are shown in table 1. Two basal blood samples were taken, as described earlier, at 0900 h (baseline 2). Dexamethasone 1 mg was given orally at midnight and a second specimen was taken at 0900 h the following morning. Dexamethasone was then administered in the dose of 0.5 mg six-hourly for two days whereafter a final blood sample was taken on the morning of the third day. Plasma ACTH was assayed in all samples and, in the same batch, plasma taken two weeks previously was reassayed for ACTH (baseline 1). Plasma cortisol and DHEAS were also measured. Cortisol was markedly suppressed and DHEAS partially suppressed after 1 mg dexamethasone, the latter showing further suppression to a very low level after 4 mg dexamethasone. ACTH, surprisingly, showed no significant suppression even after 4 mg dexamethasone. For this reason serial dilutions of the patitent's serum were made and reassayed for ACTH. 100 μl, 75 μl and 50 μl samples gave readings of 370 pg/ml, 240 pg/ml and 115 pg/ml respectively. Since the serum component did not dilute in parallel it was unlikely to be ACTH, but rather a non-specific interference in the assay. Similarly, basal values for ACTH, originally 120 pg/ml and 145 pg/ml were found to be 140 and 165 pg/ml in a subsequent assay and blood taken on a second occasion (predexamethasone) gave a reading of 230 and 250 pg/ml, but when a 100 μl of this serum was tested for validation of the assay a reading of 370 pg/ml was obtained.

DISCUSSION

There is considerable evidence implicating adrenocortical hyperactitvity in patients with polycystic ovarian disease (Leventhal and Scommegna, 1963; Mahesh and Greenblat, 1964; Gabrilove *et al.*, 1965; Smith *et al.*, 1965; Kirschner and Jacobs, 1971; Givens *et al.*, 1975; Duignan, 1976; Yen *et al.*, 1976; Lachelin *et al.*, 1979). Whether this is due primarily to an adrenal factor, eg. an enzyme deficiency, or to a pituitary dysfunction, the possibility exists that ACTH secretion may be elevated. In the present study basal ACTH values were similar to controls i.e. less than 38 pg/ml in six of eight patients with polycystic ovaries. One patient had ACTH levels marginally above the highest value for the control group, but well within the normal range previously determined in our laboratory. In a second patient, consistently elevated ACTH concentrations were found without any clinical evidence of adrenocortical

hyperactivity and inexplicably high ACTH values were unaffected by doses of dexamethasone which suppressed both F and DHEAS to low or unmeasurable levels. Further study showed these apparently high levels to be due to a serum component which interacted with antiserum in ACTH assay, giving falsely elevated results.

Recently, 6.6% of normal patients were reported to have elevated plasma ACTH as quantitated by the CIS kit (Howe and Smeaton, 1979). This ACTH like material is unlikely to be biologically active as it is not suppressed by dexamethasone, and cortisol production was normal in these subjects. The interfering factor is presently being investigated by the manufacturer and several laboratories.

From our limited study it is therefore concluded that plasma ACTH concentrations are normal in patients with polycystic ovaries.

BIBLIOGRAPHY

Berson S. A., Yalow R. S.: *J. Clin. Invest., 47,* 2725, 1968.
Buster J. E., Abraham G. E.: *Analytical Letters, 5,* 543, 1972.
Carr P. J., Millar R. P., Crowley H.: *Ann. Clin. Biochem., 14,* 207, 1977.
Duignan N. M.: *Br. J. Obst. Gyn., 83,* 593, 1976.
Drekter I. J.: *J. Clin. Endocr., 12,* 55, 1952.
Few J. D.: *J. Endocrinol., 22,* 31, 1961.
Gabrilove J. L., Sharma D. C., Dorfman R. I.: *New Engl. J. Med., 272,* 1189, 1965.
Givens J. R., Anderson R. N., Ragland J. B., Wiser W. L., Umstot E. S.: *J. Clin. Endocr. Metab., 40,* 988, 1975.
Howe L., Smeaton T.: *Clin. Chem., 25,* 5, 1979.
Katz M., Cohen B. M., Carr P. J.: *The polycystic ovary: An explanation for the mechanism of resumption of ovulatory menstrual cycles after bilateral ovarian wedge resection.* Submitted to *Clin. Endocrin.*
Kirshner A., Jacobs J.: *J. Clin. Endocr. Metab., 33,* 199, 1971.
Lachelin G. C. L., Barnett M., Hopper B., Brink G., Yen S. S. C.: *J. Clin. Endocr. Metab., 49,* 892, 1979.
Leventhal M. L., Scommegna A.: *Am. J. Obst. Gyn., 87,* 445, 1963.
Mahesh V. B., Greenblatt R. B.: *Rec. Prog. Horm. Res., 20,* 341, 1964.
Midgley A. R. Jr.: *Endocrinology, 79,* 10, 1966.
Millar R. P., Kewley C.: *S. Afr. Med. J., 50,* 1021, 1975.
Smith K. D., Steinberger E., Perloff W. H.: *Am. J. Obst. Gyn., 93,* 994, 1965.
Yen S. S. C., Chaney C., Judd H. L.: *Functional aberrations of the hypothalamic-pituitary systsem in polycystic ovary syndrome: a consideration of the pathogenesis.* In: *The Endocrine Function of the Human Ovary.* James V. H. T., Serio M., Giusti G. (eds.), Academic Press, London, 373, 1976.