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Evaluation of the hypothalamic–pituitary–adrenal axis in patients with antiphospholipid syndrome

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SUMMARY

Introduction: Hypothalamic–pituitary–adrenal (HPA) axis insufficiency is the most common endocrine disorder in patients with antiphospholipid syndrome (APS). Primary adrenal failure because of venous thrombosis and/or adrenal haemorrhage is the leading diagnosis, while another possible mechanism is autoimmune adrenal failure. Prospective evaluation of the HPA axis in patients with APS has not been previously performed. **Aims:** To evaluate the HPA axis in patients with APS. **Methods:** Ambulatory patients (age 18 years and older) with APS were given a symptom questionnaire. Baseline aldosterone, corticotropin (ACTH) and adrenal cortex autoantibodies (ACA) were measured. Cortisol was measured at baseline and after 1-mcg ACTH stimulation. **Results:** In all, 24 patients (18 women/6 men; mean age 44.6 ± 16.1 years) participated in the study. Of these, 21 had primary APS with disease duration of 5.8 ± 6.2 years. Baseline cortisol level was 12.6 ± 4.2 mg/dl (normal 7–25). After ACTH stimulation, it was 24.7 ± 4.1 mg/dl and 22.8 ± 7.4 mg/dl at 30 and 60 min respectively. All patients had a stimulated cortisol level of at least 18 mg/dl, although three patients had stimulated cortisol between 18 and 20 mg/dl, one of which reported previous inhaled steroid treatment. Weakness, dizziness and nausea were reported at baseline by 50%, 38% and 25% of the patients respectively. ACA were negative in all patients examined. **Conclusions:** In our cohort, patients with APS did not have HPA axis insufficiency. Partial adrenal insufficiency could not be excluded in two patients. Further longitudinal studies are needed to determine the significance of periodic evaluation of the HPA axis in patients with APS.

What's known
Autoimmune diseases tend to overlap. In particular, antiphospholipid syndrome is associated with primary, autoimmune adrenal failure. The gold standard test used to diagnose adrenal insufficiency is the synacten test. An additional, relatively new tool is the detection of adrenal autoantibodies in the patients' sera.

What's new
In this work, we screened patients with APLA syndrome for adrenal insufficiency using the 1-mcg ACTH stimulation. Although the results of this screening were negative, i.e. no adrenal insufficiency was detected, the screening approach should be considered in future patients with autoimmune diseases.

Introduction

The antiphospholipid syndrome (APS) is an acquired thrombophilic disorder in which autoantibodies to various phospholipids and phospholipid-binding proteins are produced, resulting in arterial and/or venous thrombosis. The clinical manifestations vary, but may involve any organ system in the body (1).

Adrenal insufficiency is probably the most common endocrinological manifestation in patients with APS. Thrombosis of the adrenal vein and/or bilateral adrenal haemorrhage can cause acute adrenal failure, while an autoimmune process can lead to chronic, slowly progressive, adrenal insufficiency (2–4). Pituitary or hypothalamic insufficiency resulting from secondary adrenal failure has been anecdotally reported (5,6). Given the different pathogenetic mechanisms, adrenal insufficiency may present with acute and dramatic symptoms or progress insidiously, resulting in a vague, non-specific clinical picture (7,8).

The 1-mcg short adrenocorticotropin (ACTH) stimulation test is used for dynamic evaluation of the hypothalamic–pituitary–adrenal (HPA) axis and is comparable to the more standardised 250-mcg ACTH test (9–11). A relatively new tool for evaluating the HPA axis is adrenal cortex autoantibodies (ACA), which are currently the most reliable serological marker of adrenal insufficiency (12–14).

Prospective evaluation of the HPA axis in patients with APS has not been previously reported. This study evaluated the HPA axis in patients with APS using clinical and biochemical parameters including the 1-mcg ACTH stimulation test, in combination with adrenal antibodies.

Methods

This prospective study was performed at a secondary referral hospital, an 800-bed, university-affiliated, medical centre. Ambulatory patients who were at

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least 18 years of age, diagnosed with APS according to the revised Sapporo criteria (15) were recruited. Clinical data were obtained from the medical chart and during a personal interview. Baseline blood samples were measured at 08:00 AM, after an overnight fast. Tests included full chemistry, white blood cell count, morning cortisol, ACTH, aldosterone, and thyroid function tests. Cortisol was also measured 30 and 60 min after intravenous administration of 1-mcg synthetic corticotropin (Synacten, Novartis Pharma, Basel, Switzerland). Cortisol and ACTH were measured by chemiluminescence immunoassay using immulite® 2000 (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). ACA were tested by immunofluorescence on human adrenal cortical tissue, as described previously (12). Antibodies to 21-hydroxylase were tested by immunoprecipitation assay (RSR Ltd., Cardiff, UK), as previously described (13).

Patients who had undergone steroid treatment for 2 weeks or longer within 6-months of the study were excluded. The study was approved by the Ethical Committee of the Medical Center. All patients provided written informed consent.

Statistical analysis

Continuous parameters are expressed as mean ± SD and categorical parameters are expressed as percentages. The statistical significance was set at 0.05 and analyses were performed using the SPSS for Windows software, version 14.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 24 patients (18 women/6 men; mean age 44.6 ± 16.1 years) participated in the study. Of these, 21 had primary APS and 3 had secondary APS. The main epidemiological, clinical and laboratory data of our series are summarised in Tables 1 and 2.

Baseline and stimulated cortisol levels were within the expected range (Table 3). All patients had peak cortisol levels above 18 mcg/dl and 88% had a stimulated cortisol level higher than 20 mcg/dl (Fig. 1). Twelve percent of the patients (Nos. 7, 8 and 21) had stimulated cortisol levels between 18 and 20 mg/dl; Patient No. 7 had been treated with steroid injections to the knee and Patient No. 8 had been treated with inhaled steroids more than 6 months prior to the study. This patient also had a baseline cortisol level of 3.9 mcg/dl and a below normal ACTH level of 6 pg/ml. Patient No. 21 is a 32-year old female, steroid-treatment naive, who reported dizziness and low blood pressure. She had normal baseline cortisol of 11.6 mg/dl, normal aldosterone and a normal ACTH level of 24 pg/ml. Adrenal cortex and 21-hydroxylase antibodies were tested in 11 of our patients (46%) and found to be negative in all. Unfortunately, we do not have adrenal antibody status for these three patients.

Fasting blood glucose levels were below 80 mg/dl in 25% of our patients, yet all had stimulated cortisol above the level of 20 mcg/dl. No patient had hyponatremia, hyperkalemia, or eosinophilia above 1000 K/dl.

Weakness, dizziness and nausea were reported at baseline by 50%, 38% and 25% of the patients respectively, while low blood pressure, weight loss and darkening of the skin were reported by < 25%. There was no association between the number and type of 'Addisonian' symptoms and the peak cortisol response to corticotropin stimulation (data not shown).

Table 1 Clinical data of 24 patients with antiphospholipid syndrome

Clinical parameters	Mean ± SD (%)
Women/men	18/6 (75/25)
Age [mean; range (years)]	44.6 ± 16.1; 21–76
Primary/secondary APS	21/3 (88/12)
Duration of APS [mean; median (years)]	5.8 ± 6.2; 4.0
No. of APS-defining symptoms	1.4 ± 0.6
DVT/PE/CVA/rec. abortions/other	7/5/5/5/9
Other autoimmune diseases (Lupus/others)	3/4 (13/17)
Anticoagulant/antiplatelet therapy	17/11 (71/46)

APS, antiphospholipid syndrome; CVA, cerebrovascular accident; DVT, deep vein thrombosis; PE, pulmonary embolism; rec. abortions, recurrent abortions.

Table 2 Laboratory data of 24 patients with antiphospholipid syndrome

Laboratory test	Mean ± SD (normal values)
Sodium (mEq/l)	139.6 ± 2.0 (135–145)
Potassium (mEq/l)	4.4 ± 0.4 (3.5–5)
Creatinine (mg/dl)	1.0 ± 0.2 (0.5–1.2)
Glucose (mg/dl)	92.7 ± 18.7 (70–110)
Haemoglobin (g/dl)	13.3 ± 1.5 (12–16)
Eosinophils (K/dl)	270.4 ± 173.0 (0–600)
Thyrotropin (mU/l)	2.2 ± 2.4 (0.23–4)
Free thyroxine (ng/dl)	1.8 ± 2.7 (0.8–2)
Anticardiolipin antibodies (pos/neg; %)	16/8 (67/13)
Lupus anticoagulant (pos/neg; %)	20/4 (83/17)

Table 3 Clinical and laboratory characteristics of the hypothalamic–pituitary–adrenal axis in 24 patients with antiphospholipid syndrome

Laboratory test	Mean ± SD (normal values)
Cortisol (baseline) (mcg/dl)	12.6 ± 4.2 (7–25)
Cortisol (30 min*) (mcg/dl)	24.7 ± 4.1
Cortisol (60 min*) (mcg/dl)	22.8 ± 7.4
Aldosterone (pg/ml)	57.7 ± 49.2 (10–160)
ACTH (pg/ml)	18.3 ± 9.7 (9–52)
Adrenal cortex antibodies	0/10
21-Hydroxylase antibodies	0/10
No. of 'Addisonian' symptoms†	1.5 ± 1.4
Previous steroid treatment‡	5 (21)

*Cortisol levels were measured 30 and 60 min after 1-mcg synthetic adrenocorticotropin; †Addisonian symptoms included dizziness, weakness, nausea, darkening of the skin, low blood pressure (< 100/80 mmHg) and weight loss; ‡previous steroid treatment denotes steroid > 6 months before study. ACTH, adrenocorticotropin.

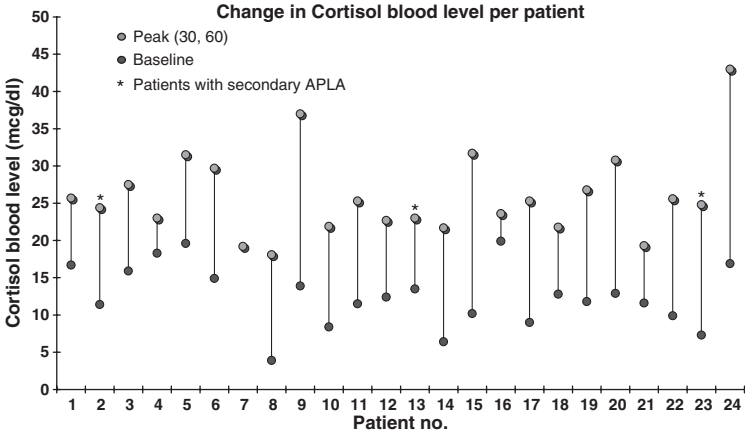

Figure 1 Cortisol blood levels before and after 1-mcg adrenocorticotropin stimulation in 24 patients with antiphospholipid syndrome

Discussion

Adrenal insufficiency, mostly primary, is considered to be the most common endocrine manifestation in patients with APS, although its prevalence in APS patients is unknown (2,3). The association between adrenal insufficiency and APS, might develop rapidly in the course of catastrophic APS, yet, a more protracted course can occur (4). Autoimmune primary adrenal failure, which is the prevalent form of adrenal insufficiency in the western world (7), might be under diagnosed in patients with APS, especially in the clinical context of chronic, slowly progressive adrenal failure.

In this study, we prospectively evaluated the HPA axis in 24 patients with APS, using the 1-mcg ACTH stimulation test and other clinical parameters to identify patients with 'subclinical' adrenal insufficiency.

Currently, there is no consensus regarding the diagnosis of 'subclinical' or latent adrenal insufficiency, although some definitions have been proposed (14). The criteria for overt adrenal insufficiency, although still in some dispute in the literature, define stimulated plasma cortisol level of < 18 mcg/dl as the cutoff point for suboptimal adrenal reserve (7,8). None of our patients had stimulated cortisol levels below 18 mcg/dl, indicating that all our patients had an intact HPA axis. Indeed, three of our patients had stimulated cortisol levels between 18 and 20 mcg/dl, with ACTH levels of 12, 6 and 24 pg/ml respectively (normal: 9–52 pg/ml). Apparently, the second patient had mild, secondary adrenal insufficiency because of previous, prolonged inhaled steroid treatment, occurring more than 6 months prior to the study. The other two patients had normal aldosterone levels (163 and 65, respectively; normal: 10–160 pg/ml) and low normal ACTH levels of 12 and 24 pg/ml (normal: 9–52 pg/ml) respectively, suggesting an intact HPA axis, although the possibility of mild, secondary adrenal failure cannot be excluded. Of note, these parameters do not support primary adrenal failure, previously reported as the dominant type of adrenal insufficiency in patients with APS (4).

A recent meta analysis argued that 30-min cortisol levels above 22 mcg/dl was the best predictor of HPA sufficiency (11). According to this criterion, three additional patients and 25% of our cohort overall, have insufficient adrenal reserve. Of note, the adrenal antibody status of two of these three patients was negative.

Plasma corticotropin concentration exceeding 100 pg/ml might indicate primary adrenal failure, albeit with a normal plasma cortisol level (7). Yet, none of our patients had an elevated plasma corticotropin level. In fact, 77% of our patients had a corticotropin level < 30 pg/ml, i.e. in the lower half of the normal range. The plasma aldosterone level, which might also be compromised in primary adrenal failure (7), was within the normal range in all our patients. Taken together, the measurement of stimulated cortisol, ACTH and aldosterone plasma levels did not detect compromised adrenal reserve in our cohort. Nevertheless, partial adrenal insufficiency could not be excluded in 8.3% of our patients.

Adrenal autoantibodies might be found in up to 90% of patients with autoimmune adrenal disease and therefore can aid in the evaluation of primary adrenal failure because of an autoimmune pathogenesis (7,12). The presence of ACA and 21-hydroxylase autoantibodies can also help in predicting subsequent adrenal failure in patients with a normal HPA axis (12–14). During the current evaluation for possible adrenal insufficiency, we screened 46% of our cohort for adrenal autoantibodies, which were negative.

Our patients had an average of 1.5 ± 1.4 'Addisonian' symptoms each; the most common were weakness, dizziness and nausea. These symptoms occurred in fewer than half of our patients and did not correlate with the biochemical test results.

Our study is the first prospective evaluation of the HPA axis in patients with APS. In addition, it is the first study that included an evaluation of adrenal antibodies in APS patients.

This study has several limitations: although the study personnel were knowledgeable and experienced in performing the corticotropin test, a technical failure involved with its preparation, possibly leading to a suboptimal cortisol response cannot be excluded. Our study did not have a comparator group that would aid in assessing the frequency of 'Addisonian' symptoms. Moreover, we assessed the integrity of the HPA axis only once for each patient. A longitudinal study with periodic evaluations of the axis could shed light on the process of developing adrenal insufficiency. In addition, measurement of dehydroepiandrosterone sulphate levels and plasma renin activity, which might have a role in assessing the HPA axis (16,17) were not included in our study.

Conclusions

In summary, we found an intact adrenal axis in patients with APS who were evaluated using 1-mcg corticotrophin stimulation. Additional longitudinal studies are needed to determine the significance of periodic evaluation of the HPA axis in patients with APS.

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Author contributions

Pnina Rotman-Pikielny: concept/design, data collection, data analysis/interpretation, drafting article, critical revision of article, approval of article. Menachem S. Shapiro: concept/design, critical revision of article, approval of article. Martin Ellis: data collection, critical revision of article, approval of article. Corrado Betterle: data analysis/interpretation, critical revision of article, approval of article. Yair Levy: concept/design, data analysis/interpretation, critical revision of article, approval of article.

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