Adrenal Gland Hypofunction in Active Polymyalgia Rheumatica. Effect of Glucocorticoid Treatment on Adrenal Hormones and Interleukin 6

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ABSTRACT. Objective. To evaluate hypothalamic-pituitary-adrenal (HPA) axis function in patients with recent onset polymyalgia rheumatica (PMR) not previously treated with glucocorticoids; and to detect possible correlations between adrenal hormone levels, interleukin 6 (IL-6), and other acute phase reactants at baseline and during 12 months of glucocorticoid treatment.

Methods. Forty-one PMR patients of both sexes with recent onset disease and healthy sex and age matched controls were enrolled into a longitudinal study. Patients were monitored for serum cortisol, dehydroepiandrosterone sulfate (DHEAS), androstenedione (ASD), and clinical and laboratory measures of disease activity such as C-reactive protein and IL-6 concentrations at baseline and after 1, 3, 6, 9, and 12 months of glucocorticoid treatment. To assess dynamic HPA axis function, serum cortisol and plasma adrenocorticotropic hormone (ACTH) levels were evaluated in another 8 patients with recent onset PMR not treated with glucocorticoids in comparison to controls after challenge with ovine corticotropin releasing hormone (oCRH) test. In addition, serum cortisol and 17-hydroxyprogesterone (17-OHP) levels were evaluated after stimulation with low dose (1 µg) intravenous ACTH.

Results. Serum cortisol and ASD levels of all PMR patients at baseline did not differ from controls. During followup, cortisol levels dropped significantly at one and 3 months. Serum DHEAS levels in all patients were significantly lower than in controls at baseline. In female PMR patients a significant correlation was found at baseline between cortisol levels and duration of disease. Serum concentrations of IL-6 at baseline were significantly higher in PMR patients than in controls. During 12 months of glucocorticoid treatment IL-6 levels dropped significantly at one month; thereafter they remained stable and did not increase again despite tapering of the glucocorticoid dose. After oCRH stimulation, a similar cortisol response was found in patients and controls. After ACTH administration, a significant corticosterone peak was detected in patients and controls, whereas no significant difference in cortisol area-under-the-curve (AUC) was found between the groups. In contrast, ACTH induced a significantly higher (p < 0.05) peak of 17-OHP and AUC in PMR patients than in controls.

Conclusion. This study found reduced production of adrenal hormones (cortisol, DHEAS) at baseline in patients with active and untreated PMR. The defect seems mainly related to altered adrenal responsiveness to the ACTH stimulation (i.e., increased 17-OHP), at least in untreated patients. The 12 month glucocorticoid treatment of patients reduced the production of inflammatory mediators (i.e., IL-6) in a stable manner that persisted after glucocorticoids were tapered. (J Rheumatol 2002;29:748–56)

Key Indexing Terms:
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HYPOTHALAMIC-PITUITARY-ADRENAL AXIS
GLUCOCORTICOID
INFLAMMATION
ARTHITIS
INTERLEUKIN 6

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Polymyalgia rheumatica (PMR) is a common disorder in the elderly characterized by aching and morning stiffness in the neck, shoulders, and pelvic girdle, along with constitutional symptoms (malaise, weight loss, fever) and marked serologic acute phase response. Although PMR occurs in patients older than 50 years of age and PMR incidence increases with age, age-associated pathogenic factors are not yet known. The natural decline of several hormones, including dehydroepiandrosterone/sulfate (DHEA/DHEAS) and androstenedione (ASD), with aging may represent one such factor. The decrease of adrenal/gonadal hormones is different in both sexes (in healthy subjects), for example cortisol and 17-hydroxyprogesterone (17-OHP) decrease in women but not in men.

However, in both sexes, serum cortisol levels are relatively low in relation to plasma adrenocorticotropic hormone (ACTH), which indicates that despite increased ACTH, the production of cortisol decreases during aging. Nevertheless, serum cortisol levels remain relatively high in relation to serum levels of other adrenal and gonadal hormones during aging. In addition, aging is characterized by altered innate immune system function with a loss of phagocytic capacity and an increase of “early” cytokines such as interleukin 6 (IL-6) and tumor necrosis factor (TNF). Recently, it was reported that DHEA and ASD have a direct inhibitory effect on IL-6 secretion in monocytes and macrophages. All these findings might support a possible link between endocrinosenescence and immunosenescence in the pathogenesis of PMR.

The abrupt onset of PMR, with clinical features similar to the steroid withdrawal syndrome (i.e., musculoskeletal pain, malaise, fever) or adrenal insufficiency, and the dramatic and rapid disappearance of these symptoms after glucocorticoid administration, may be a strong clinical argument for an altered function of the hypothalamic-pituitary-adrenal (HPA) axis in these patients. Plasma IL-6 concentrations and clinical symptoms during 14 months of glucocorticoid therapy are correlated in patients with PMR. However, no dynamic studies are available on HPA axis function in patients with recent onset PMR not previously treated with glucocorticoids and in relation to their inflammatory condition (i.e., increased IL-6).

In this study, female and male patients with recent onset PMR were monitored for adrenal hormones (cortisol, DHEAS, ASD) and laboratory measures of disease activity, including IL-6 concentrations, during a 12 month period of glucocorticoid treatment. To assess HPA axis function, cortisol and ACTH were evaluated in patients with recent onset PMR not treated with glucocorticoid and in healthy age matched controls after stimulation with ovine corticotropin releasing hormone (oCRH). In addition, cortisol and 17-OHP levels were evaluated after stimulation with low dose intravenous ACTH.

Materials and Methods

Patient selection. Forty-one patients of both sexes with active PMR were enrolled in the study after giving informed consent. Patients were clinically evaluated by a rheumatologist at the Reggio Emilia Hospital; diagnosis of PMR was based on the criteria of Chuang, et al. Patients with clinical and/or histological evidence of temporal arteritis were excluded. All selected patients had recent onset PMR and had never been treated with glucocorticoids or hormone replacement. Nonsteroidal antiinflammatory drugs were withdrawn 6 days before the study. Sex and age matched healthy controls were analyzed for comparison. Blood samples were collected by venipuncture between 10:00 and 12:00 AM and serum was immediately stored at −80°C until analysis. These 41 patients had prospective followup for at least one year. Patients were clinically assessed by the same physician at presentation, monthly for the first 6 months, then every 3 months during the followup period. All patients received the same schedule of prednisone treatment starting at 17.5 mg/day (occasionally this needed to be increased to 25 mg/day to completely relieve discomfort), administered before breakfast. The initial dosage was then reduced after one month if symptoms had resolved. Small monthly decreases of 1–5 mg were successively scheduled. Serial blood samples were collected between 10:00 and 12:00 AM at baseline, one month after the beginning of therapy, and at 10–12 week intervals during the followup (12 months). A further group of 8 female patients with recent onset untreated PMR were recruited at the Division of Rheumatology of the University of Genova for analysis of HPA axis function, after informed consent was obtained. Eight healthy sex and age matched controls were also analyzed for comparison.

Laboratory evaluations. A standardized medical data collection form was used at every visit. Age, sex, location of aching and morning stiffness, the presence of systemic manifestations, dosage and duration of glucocorticoids, and the development of relapses and recurrences were recorded. The cumulative prednisone dose was computed. The presence of peripheral synovitis (swelling and tenderness of the joints) was carefully assessed at each visit. Joint radiography was performed in all patients with joint swelling at some time during the course of illness. Relapse and recurrence were considered present if articular signs or symptoms occurred (usually with an erythrocyte sedimentation rate (ESR) > 30 mm/h) in a patient receiving glucocorticoids, or after discontinuation of treatment, respectively. All patients were also evaluated at diagnosis and during the followup for the 1987 modified American Rheumatism Association (ARA) criteria for RA. At baseline and during followup, laboratory measures including ESR, C-reactive protein (CRP), mean hemoglobin (Hb), and fibrinogen levels in patients were evaluated by standard methods. IL-6 concentrations were evaluated by immunoassay (Duoset ELISA Kit, R&D Systems, Minneapolis, MN, USA). Results were expressed as pg/ml. Assay sensitivity was 0.2–0.4 pg/ml. Serum IL-6 levels were 1.4 ± 0.9 pg/ml in the 19 controls.

In the longitudinal study, cortisol was assayed by chemiluminescence assay (Immunolite, DPC, Los Angeles, CA, USA). Assay sensitivity was 5.52 nmol/l. Intraassay and interassay coefficients of variation were 6.1% and 8.2% at 320.5 nmol/l and 5.2% and 6.2% at 496.8 nmol/l. Cross reactivity with prednisone was 6.1%. DHEAS was assayed by enzyme immunoassay (EIA) (Biochem Immunosystems Italia, Casalecchio di Reno, Bologna, Italy). Assay sensitivity was 0.15 µmol/l. Intraassay and interassay coefficients of variation were 2.7% and 3.1% at 1.35 µmol/l and 7.4% and 8.8% at 10.8 µmol/l. ASD was assayed by radioimmunoassay (Dixonson, Minneapolis, MN, USA). Assay sensitivity was 0.1 nmol/l. Intraassay and interassay coefficients of variation were 5.6% and 9.8% at 2.4 nmol/l and 4.3% and 6.0% at 8.1 nmol/l.

In the dynamic study to test the HPA axis, cortisol was evaluated as described above. 17-OHP was assayed by chemiluminescence assay (ImmunoLite, DPC). Assay sensitivity was 0.02 nmol/l. Intraassay and interassay coefficients of variation were 4.3% and 8.0% at 0.77 nmol/l and 5% and 7% at 2.23 nmol/l. ACTH was detected by IRMA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Assay sensitivity was 0.22 ng/ml.
RESULTS
Characteristics of the study population. Complete clinical and demographic data are shown in Table 1. Throughout the followup period, no patient fulfilled the modified 1987 ARA criteria for RA, and no clinical evidence of joint deformity at baseline was observed12.

Longitudinal study. Adrenal hormone concentrations. Serum cortisol levels of all PMR patients at baseline did not differ from the cortisol levels of controls. However, mean baseline levels were significantly lower in female patients compared to female controls (p < 0.05), a difference not found in male subjects (Table 2). During the followup, serum cortisol levels at one and 3 months were found to be reduced compared to baseline (p < 0.001 and p < 0.05, respectively). At 9 and 12 months, however, serum cortisol levels were restored in female patients compared to values at one month (p < 0.01 and p < 0.05, respectively) (Table 3).

Table 1. Complete clinical and demographic data of the PMR patients included in the longitudinal and dynamic studies (basal values) (no significant differences were found).

<table>
<thead>
<tr>
<th></th>
<th>All PMR Patients</th>
<th>Female PMR Patients</th>
<th>Male PMR Patients</th>
<th>Female Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal study</td>
<td>n = 41</td>
<td>n = 28</td>
<td>n = 13</td>
<td>—</td>
</tr>
<tr>
<td>Mean age, yrs ± SD</td>
<td>71.2 ± 6.2</td>
<td>71.4 ± 8.2</td>
<td>72.1 ± 6.1</td>
<td>—</td>
</tr>
<tr>
<td>Mean PMR duration, mo ± SD</td>
<td>2.6 ± 0.2</td>
<td>2.4 ± 0.3</td>
<td>2.9 ± 0.6</td>
<td>—</td>
</tr>
<tr>
<td>Mean starting dose of prednisone, mg/day</td>
<td>17.4 ± 2.1</td>
<td>18.3 ± 2.1</td>
<td>16.8 ± 2.5</td>
<td>—</td>
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<tr>
<td>Dynamic study</td>
<td>n = 8</td>
<td>n = 8</td>
<td>n = 8</td>
<td>—</td>
</tr>
<tr>
<td>Mean age, yrs ± SD</td>
<td>—</td>
<td>72.6 ± 1.8</td>
<td>72.9 ± 4.0</td>
<td>—</td>
</tr>
<tr>
<td>Mean PMR duration, mo ± SD</td>
<td>—</td>
<td>2.5 ± 0.5</td>
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</tbody>
</table>
In female patients, cortisol and DHEAS levels were significantly correlated with ESR (p < 0.001 and p < 0.05, respectively), whereas CRP was strongly correlated with cortisol, DHEAS, and ASD levels (p < 0.001, p < 0.005, p < 0.001). In male patients, cortisol levels were significantly correlated (negative) with CRP (p < 0.01) (data not shown). Finally, in both female and male PMR patients, cortisol and ASD were significantly correlated (negative) with fibrinogen levels (p < 0.0001, p < 0.05) (data not shown).

IL-6 concentrations and correlations. Serum concentrations of IL-6 at baseline were significantly higher in PMR patients than in healthy controls (25.9 ± 4.6 versus 1.4 ± 0.9 pg/ml; p < 0.01) (Table 4). Serum IL-6 levels decreased significantly after the beginning of glucocorticoid treatment (one month) in all PMR patients (p < 0.05), with evident differences between female and male patients (even if limited by the lower sample size) (p < 0.05 and p < 0.01, respectively) (Table 4). IL-6 levels remained stable during the followup in all patients (Figure 4).

Regarding the correlations between IL-6 levels and adrenal hormones, a significant positive correlation was observed with cortisol in all PMR patients (p < 0.006), whereas DHEAS was found to be significantly correlated (negative) with IL-6 only in female patients (p < 0.05) (data not shown). Using the values at the different time points during the 12 month followup, IL-6 levels were significantly correlated with ESR and serum levels of CRP and fibrinogen in both male and female patients (p < 0.0001) (data not shown).

## Table 2. Basal serum values of cortisol, DHEAS, and ASD in PMR patients and controls in the longitudinal study.

<table>
<thead>
<tr>
<th></th>
<th>All Healthy Controls, n = 50</th>
<th>All PMR Patients, n = 41</th>
<th>Female PMR Patients, n = 30</th>
<th>Male PMR Patients, n = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortisol, nmol/l ± SE</strong></td>
<td>460.6 ± 21.5</td>
<td>460.6 ± 23.1</td>
<td>387.8 ± 30.5</td>
<td>485.2 ± 26.8*</td>
</tr>
<tr>
<td><strong>DHEAS, µmol/l ± SE</strong></td>
<td>2.2 ± 0.4</td>
<td>1.25 ± 0.12</td>
<td>1.82 ± 0.33</td>
<td>0.97 ± 0.07***</td>
</tr>
<tr>
<td><strong>ASD, nmol/l ± SE</strong></td>
<td>4.2 ± 0.4</td>
<td>5.7 ± 0.46</td>
<td>4.3 ± 0.6</td>
<td>4.9 ± 0.37</td>
</tr>
</tbody>
</table>

* Versus female healthy controls p < 0.05; ** versus healthy controls p < 0.01; *** versus female healthy controls and male PMR patients p < 0.01; † versus healthy controls p < 0.05.

## Table 3. Serum cortisol, DHEAS, and ASD levels during followup of the PMR patients during glucocorticoid treatment.

<table>
<thead>
<tr>
<th></th>
<th>Month</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Cortisol, nmol/l ± SE</strong></td>
<td></td>
</tr>
<tr>
<td>All PMR patients, n = 41</td>
<td>460.6 ± 21.5</td>
</tr>
<tr>
<td>Female, n = 28</td>
<td>485.2 ± 26.8</td>
</tr>
<tr>
<td>Male, n = 13</td>
<td>408.5 ± 43.6</td>
</tr>
</tbody>
</table>

* versus baseline p < 0.001; ** versus baseline p < 0.05; *** versus month 1 p < 0.01; † versus month 1 p < 0.05; †† versus baseline p < 0.05; †versus baseline p < 0.01; †versus baseline p < 0.05.

In female patients, cortisol and DHEAS levels were significantly correlated with ESR (p < 0.001 and p < 0.05, respectively), whereas CRP was strongly correlated with cortisol, DHEAS, and ASD levels (p < 0.001, p < 0.005, p < 0.001). In male patients, cortisol levels were significantly correlated (negative) with CRP (p < 0.01) (data not shown). Finally, in both female and male PMR patients, cortisol and ASD were significantly correlated (negative) with fibrinogen levels (p < 0.0001, p < 0.05) (data not shown).

**Dynamic study. HPA axis stimulation tests.** After oCRH stimulation, a significant increase of ACTH levels from basal values (p < 0.05) was found in both PMR patients and controls (Figure 5A). However, the ACTH AUC after oCRH was found to be similar in both groups (see inset, Figure 5A). After oCRH stimulation, a similarly significant cortisol peak (p < 0.01) was found in patients and controls (Figure 5B), whereas cortisol AUC were similar between the groups (see inset, Figure 5B).

As expected, after ACTH administration, significant cortisol peaks (p < 0.01) were detected in PMR patients and controls (Figure 5A), whereas no significant difference in cortisol AUC was found between the groups (see inset, Figure 5B).

After low dose ACTH stimulation, both groups showed a significant increase of 17-OHP (p < 0.05) versus basal levels (Figure 6B). However, the 17-OHP peak and 17-OHP AUC
were significantly higher (both \( p < 0.05 \)) in patients compared to controls (see Figure 6B and inset, respectively). Further, baseline levels of 17-OHP were significantly higher in patients than in controls (\( p < 0.05 \)).

All PMR patients showed a normal plasma cortisol inhibition (< 138 nmol/l) following the dexamethasone test.

**DISCUSSION**

By considering the inflammatory status, a lower than expected basal production of adrenal steroids was observed in active and glucocorticoid-untreated patients with PMR, particularly in female patients. The 12 month glucocorticoid treatment of PMR patients, by reducing in a stable manner the inflammatory mediator levels (i.e., IL-6) that persist even after tapering of glucocorticoids, at the same time restored baseline levels of serum adrenal hormones.

A significant increase of 17-OHP levels in both basal condition and after ACTH stimulation was found in patients with recent onset untreated PMR compared to healthy age matched controls. Since 17-OHP represents a precursor of cortisol biosynthesis at the adrenal level, a possible partial impairment of the enzyme (21\( \alpha \)-hydroxylase) may be
present that leads to accumulation of the precursor 17-OHP.

The reasons for a functional 21α-hydroxylase impairment in PMR may include genetic defects, or an age related increase of serum TNF in healthy women, or elevated serum IL-6 and TNF levels during chronic systemic inflammatory stimuli (i.e., psychosocial stressors and variables such as coping and personality), and chronic systemic inflammatory stimuli (i.e., chronic infections) characterized by elevated serum IL-6 and TNF levels. As shown, IL-6 and ACTH act synergistically to stimulate direct release of corticosterone from the adrenal glands.

Thus the continuous stimulation of the HPA axis at different levels might make the system unresponsive to the acute rise of these cytokines during inflammatory exacerbation of a disease, as in rheumatoid arthritis (RA). The changes observed in serum levels of adrenal hormones in the patients with recent onset untreated PMR might suggest an overall significant shift to cortisol synthesis (although not sufficient as antiinflammatory) in relation to DHEAS, as observed in patients with PMR or RA treated with glucocorticoid.

The reduction of serum DHEAS is a general feature of chronic inflammatory diseases, and the enzymes involved in the synthesis of DHEAS and ASD (17α and 17,20-hydroxylase) are suppressed during aging and in response to inflammatory mediators such as IL-1 or even by transforming growth factor-β. Thus, during aging and under systemic inflammation, as observed during recent onset of PMR, low DHEAS and normal cortisol serum levels may be expected. In addition, since DHEA (the nonsulfated adrenal hormone) inhibits IL-6 secretion the chronic reduction of this hormone in PMR patients might represent a further factor for increased serum IL-6 levels.

A recent study analyzed the interrelation between inflammatory cytokines (IL-6, TNF) and adrenal hormones (cortisol, DHEAS, ASD) in more than 100 PMR patients with both new onset and chronic disease. Serum levels of cortisol, DHEAS, and ASD were analyzed in all PMR patients in relation to mean daily prednisone dose during the 12 months of treatment.

Figure 3. Serum cortisol, DHEAS, and ASD variations in all PMR patients in relation to mean daily prednisone dose during the 12 months of treatment.

Figure 4. Serum IL-6 and CRP levels and ESR in all PMR patients in relation to mean daily prednisone dose during the 12 months of treatment.
Table 4. IL-6 serum level variations during the 12 months of glucocorticoid treatment in all PMR patients and selected female and male patient groups.

<table>
<thead>
<tr>
<th>Month</th>
<th>IL-6, pg/ml ± SE</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>All PMR patients, n = 41</td>
</tr>
<tr>
<td>0</td>
<td>25.96 ± 4.62</td>
</tr>
<tr>
<td>1</td>
<td>6.37 ± 2.6</td>
</tr>
<tr>
<td>3</td>
<td>6.82 ± 2.62</td>
</tr>
<tr>
<td>6</td>
<td>7 ± 2.39</td>
</tr>
<tr>
<td>9</td>
<td>7.63 ± 3.8</td>
</tr>
<tr>
<td>12</td>
<td>5.74 ± 2.63</td>
</tr>
</tbody>
</table>

* Versus baseline p < 0.05; ** versus baseline p < 0.01; *** versus baseline p < 0.05.

Figure 5. A. Mean (± SE) ACTH response to IV oCRH (arrow, 1 mg/kg body weight) over 120 min in 8 female patients with recent onset PMR and 8 healthy controls (CTR). Inset: ACTH net AUC in controls and PMR patients. *p < 0.05 vs basal values. B. Mean (± SE) cortisol response to IV oCRH (arrow, 1 µg/kg body weight) over 120 min in 8 female patients with recent onset PMR and 8 healthy controls. Inset: cortisol net AUC in controls and PMR patients. *p < 0.01 vs basal values.

Figure 6. A. Mean (± SE) cortisol response to IV low dose ACTH (arrow, 1 µg) over 90 min in 8 female patients with recent onset PMR and 8 healthy controls. Inset: cortisol net AUC in controls and PMR patients. *p < 0.01 vs basal values. B. Mean (± SE) 17-OHP response to IV low dose ACTH (arrow, 1 µg) over 90 min in 8 female patients with recent onset PMR and 8 healthy controls. Inset: cortisol net AUC in controls and PMR patients. **p < 0.05 versus basal values; ***p < 0.01 between groups (17-OHP AUC).
cortisol in relation to IL-6 were found to be significantly lower in patients with chronic disease and long lasting glucocorticoid administration compared to patients with recent onset PMR and no glucocorticoid therapy. Indeed, healthy adrenal glands are capable of secreting increased amounts of endogenous cortisol necessary to control pathologic conditions in circumstances with strong activation of the HPA axis including acute stress (i.e., surgery, infections, severe interpersonal stress). However, adequate activation of the HPA axis does not appear to be the case in PMR.

Aging seems to be the predisposing condition for the observed HPA axis hyporesponsiveness and for the innate immune system dysfunction. In particular, during aging serum cortisol levels are relatively low in relation to ACTH, which indicates that despite increased ACTH, the production of cortisol decreases, and as well a loss of phagocytic capacity and increase of “early” cytokines such as IL-6 and TNF is observed. These findings might well support a possible link between endocrinosenescence and immunosenescence in the pathogenesis of PMR.

Therefore, the abrupt onset of PMR with clinical features similar to the steroid withdrawal syndrome or adrenal insufficiency (i.e., musculoskeletal pain, malaise, fever, sleepiness, anorexia, etc.) might be induced by intense stimulation and an inefficient response of the HPA axis in response to different acute stressors (i.e., surgery, infections, severe interpersonal stress) in elderly people that are already predisposed (by aging) to an inadequate adrenal and anti-inflammatory response.

We observed reduced production of adrenal hormones (i.e., cortisol, DHEAS) at baseline in patients with active and untreated PMR. The defect seems mainly related to altered adrenal responsiveness to ACTH stimulation (i.e., increased 17-OHP, possible related to CYP21A2 21-hydroxylase deficiency), at least in patients with untreated PMR. The 12 month glucocorticoid treatment of PMR patients reduces the production of inflammatory mediator levels (i.e., IL-6) in a stable manner that persists even after the tapering phase of the glucocorticoids.

REFERENCES


