Plasma testosterone, dehydroepiandrosterone sulfate, and cortisol in female patients with Huntington's disease

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Abstract

OBJECTIVE: The neuronal loss in several brain regions that characterize the progression of Huntington's disease (HD), is expected to influence the activities of hypothalamus-adrenal and hypothalamus-gonadal axes, and the changes may relate to common features of the disease, like depression and dementia. While in male HD patients low plasma testosterone levels have been reported, information on female patients is lacking.

METHODS: We assessed the plasma levels of the androgens total testosterone (TT) and dehydroepiandrosterone sulfate (DHEAS), as well as of cortisol in 41 female patients with HD, confirmed by determination of the CAG repeat number in the IT-15 gene, and searched for associations to the disease symptomatology. We also included a group of 18 females with expanded CAG repeat number in the HD gene (subjects at risk), and a group of 66 age-matched healthy females. Hormone levels of the pre- and post-menopausal subgroups were also compared separately.

RESULTS: Significant negative correlations to age were found for TT and DHEAS in both control (age range 20–71 years) and patient (age range 26 to 78 years) groups, and the calculated decline per year was around 1% for TT and 1.5% for DHEAS. There were no significant differences in hormone levels among patients, subjects at risk and controls, either in premenopausal or in postmenopausal state. The subgroup of patients with depression in their symptomatology had significantly lower TT and DHEAS levels compared to patients without depression, or to controls.

CONCLUSIONS: While TT and DHEAS seem to decline with age in female patients with HD to the same extend as for healthy females, the presence of depression, but not dementia, in their symptomatology, is connected to lower ovary-adrenal androgen levels.

ORIGINAL ARTICLE

Abbreviations

HD - Huntington's disease
TT - total plasma testosterone
DHEAS - plasma dehydroepiandrosterone sulfate

INTRODUCTION

Huntington's disease (HD) is characterized by a progressive neuronal loss, mainly in striatal and cortical areas [1], but cerebral atrophy has also been found in hypothalamic areas [2,3]. Alterations in the activities of the hypothalamus-pituitary-adrenal (HPA) and hypothalamus-pituitary-gonadal (HPG) axes can thus be expected, and both clinical and neuroendocrinological evidence suggest such abnormalities. On the other hand, common in the symptomatology of HD are dementia and depression, two states in which such alterations are well documented. The decline of androgens with age have been connected to reductions in muscle and bone mass, to depressive mood, and to cognitive impairment in a series of studies. Such symptoms are common in HD. Our group has reported low plasma testosterone levels in male patients with HD without a concomitant increase in LH levels, indicative of a dysfunction of the HPG-axis [4]. In line with this finding, a reduction in gonadotropin-releasing hormone (GnRH) immunoreactive neurons was documented in the R6/2 mouse model of HD [5].

Heuser *et al.* [6] found higher basal cortisol levels in 10 patients with HD compared to healthy controls, while Leblhuber *et al.* [7] reported higher cortisol and lower DHEAS levels in 11 male HD patients. Higher cortisol levels were related to poorer declarative memory function in healthy elderly (over 65 years) men and women, while DHEAS levels were not associated to cognitive performance [8]. A trend for higher cortisol and normal DHEAS levels, and a significant correlation between cortisol and DHEAS were reported for elderly subjects with dementia [9].

In females, more than 25% of circulating testosterone is derived from the adrenals, 25% from the ovary, and the remaining from peripheral conversion, mainly from androstenedione [10]. There is a controversy if the postmenopausal ovary is an androgen producing organ. Davison *et al.* [11] found lower TT levels in oophorectomized women aged 55 to 75 years compared to non-oophorectomized, and argue that the postpenopausal ovary is an ongoing site of testosterone production. TT and DHEAS decline steeply with age, and this decline is not affected by menopause. The decline of testosterone with age in women is considered to be also a consequence of diminishing DHEA production by the adrenals with age, since DHEA is a major source of testosterone by its transformation in peripheral tissue [12].

An overactive HPA axis, as hypothesized in depression, could lead to enhanced adrenal androgen synthesis. Indeed, elevated TT levels were found in 20 depressed women in the age range of 21 to 43 years compared to 10 controls [13], while Weber *et al.* [14] reported elevated cortisol, DHEA, and TT levels in 11 depressed women. In a large study of women aged 50 to 90 years, depressive mood was inversely associated to the DHEAS levels, but not to testosterone, estradiol, or androstendione [15].

Most studies on possible associations of androgens and dementia have been conducted on male subjects. In older females with mild to moderate Alzheimer's disease (AD), increased levels of DHEA and androsterone were found [16]. In another study on a large number of women over the age of 65 with AD, TT and DHEA levels did not differ from non-demented controls [17].

In this study, we assessed the levels of TT, DHEAS and cortisol in a group of female patients with HD, confirmed by estimation of the CAG repeat number, and searched for differences from age-marched control subjects and for associations to the symptomatology of the disease, especially to the presence of dementia and depression. We also included a group of subjects without HD symptomatology but with expanded CAG repeat number, i.e. at risk of the disease.

SUBJECTS AND METHODS

Forty-one female patients, 16 pre- and 25 post-menopausal, with a diagnosis of HD confirmed by molecular genetic analysis were studied. Their ages ranged from 26 to 78 years (mean±SD=51.4±13.9). They were outpatients of the Department of Neurology, Athens University Medical School, Eginition Hospital. We also included in the study 18 females, normally menstruating, who were genetically tested for HD and found to have a CAG repeat expansion, being at risk of developing the disease. Their ages ranged from 18 to 49 years (mean±SD=33.1±9.2).

Eleven patients were on treatment with low doses of haloperidol, usually 2 mg daily. They were not asked to discontinuate the drug, because haloperidol is not expected to influence cortisol or testosterone levels [18,19]. Indeed, when we compared their TT, cortisol, and DHEAS levels to the levels of the 30 drug-free patients (ANOVA, controlling for age), they did not differ significantly.

The CAG repeat number in the IT-15 gene was determined as described by Warner *et al.* [20]. One patient had 37 and another 34 repeats. They were included in the study since they showed overt symptomatology of the disease for two and one year respectively. In the group of subjects at risk were also included two subjects, with 34 and 39 CAG repeat number.

For the evaluation of the disease symptomatology we used the Unified Huntington's Disease Rating Scale (UHDRS, Huntington Study Group, [21]). In addition, we evaluated each patient for the presence of dementia (cutoff point 25 in the Mini-Mental State Examination),

hyperkinesias, depression (cutoff point 6 in the four items evaluating mood in the behavior assessment of the UHDRS), and psychotic features. The severity of the illness was characterized as mild, moderate, or severe, according to the HD Total Functional Capacity Scale score of Shoulson and Fahn [22].

A blood sample was taken from each subject in the morning between 8000 and 1000 hours, the plasma separated by centrifugation, and stored at –30 °C until analysis. Hormone levels were estimated using commercially available radioimmunoassay kits. For testosterone we used the kit of Adaltis (Casalecchio di Reno, Italy), for which the manufacturer gives normal value for women a mean of 0.65 ng/ml plasma. For the estimation of DHEAS and cortisol, we used the kits of Radim (Pomezia, Italy). The inter- and intra-assay coefficients of variation were less than 5%.

Statistical evaluation of the data included analysis of variance (ANOVA) with age as covariate, multiple regression analysis, and correlation tests, i.e. linear regression and the non-parametric Spearman correlation coefficient test, used as appropriate.

RESULTS

The mean values of total testosterone, cortisol, and DHEAS for patients, subjects at risk, and controls, as well as the results of the statistical evaluation, are shown in the Table. Because of the strong correlations of DHEAS and TT to age, in all ANOVAs age was used as covariate. The comparison between patients and controls showed that HD patients have normal TT, cortisol, and DHEAS levels. We then compared the data separately for pre- and post-menopausal subjects. In the comparison of the premenopausal groups, the data of the 18 subjects at risk (all premenopausal) were included. Once again, no differences were found between groups for any of the hormones measured (Table).

In searching for associations of hormone levels to specific features of the disease, we performed multiple regression analyses (forward stepwise), with dependent

Table. Plasma levels of testosterone (T), cortisol, dehydroepiandrosterone sulfate (DHEAS), all expressed in nmol/l, of female patients with Huntington's disease, subjects at risk, and healthy controls. Comparisons are also performed for subgroups according to menopausal status, and the presence of depression or dementia in the patients group. Evaluation by analysis of variance with age as covariate.

GROUP	N	AGE	T	CORT	DHEAS
Controls	66	48.8±12.9	1.75±0.75	220±98	2298±1233
Patients	41	51.4±13.9	1.54±0.57	198±71	2126±1478
F (1,104)			1.35	1.62	0.01
p			0.25	0.21	0.95
PREMENOPAUSAL					
Controls	26	35.4±7.6	2.07±0.74	208±91	2963±1273
At Risk	18	33.1±9.2	1.92±0.60	188±76	3520±1849
Patients	16	36.7±7.3	1.85±0.54	204±55	3257±1507
F (2,56)			0.69	0.33	0.55
p			0.50	0.72	0.58
POSTMENOPAUSAL	I				
Controls	40	57.5±6.6	1.53±0.68	228±103	1866±1004
Patients	25	60.8±7.1	1.35±0.51	194±80	1403±909
F (1,62)			0.86	1.35	1.54
p			0.36	0.25	0.22
PATIENTS, DEMENTIA					
NO	15	53.3±15.5	1.53±0.50	188±83	2064±1418
YES	26	50.3±13.0	1.55±0.62	203±63	2162±1538
F (1,38)			0.04	0.33	0.09
p			0.84	0.57	0.76
PATIENTS, DEPRESSION					
NO	19	50.0±14.9	1.77±0.61	219±74	2633±1747
YES	22	52.6±13.1	1.35±0.47	180±64	1689±1054
F (1,38)			5.96	2.90	5.26
p			0.019	0.096	0.027

variable TT, cortisol, or DHEAS, and independent variables age, duration of illness, severity of illness, and presence of dementia, depression, and psychotic features in the patients symptomatology. Significant associations were found only for TT to age and depression (multiple R=0.5612, F(2,38)=8.73, p<0.001), and for DHEAS to age and depression too (R=0.7165, F(2,38)=20.04, p<0.0001). In order to present this association with mean values for the subgroups with and without depression, we performed analysis of variance with age as covariate for the three hormones measured. The results are (Table) show significantly lower TT and DHEAS levels in patients with depression. The results of ANOVA with dementia as the grouping variable are also mentioned in the Table, to show the lack of association of the levels of the three hormones to dementia.

Strong negative correlations of TT to age were found in the group of 66 control subjects in the age range of 20 to 71 years (R=–0.4289, p<0.001) and the group of 41 patients with HD in the age range of 26 to 78 years (R=–0.4554, p=0.003). From the equation of the regression line for control subjects (TT=2.959-0.025×AGE), we calculated a decline of 1% per year for testosterone levels. From the regression line of the group of patients (TT=2.511-0.019×AGE), we calculated a decline of 0.95% per year, which is the same as in controls. Strong negative correlations to age were also found for DHEAS, both in controls (R=–0.5431, p<0.001) and patients with HD (R=–0.6678, p<0.001). The calculated decline for DHEAS in the control group was 1.5% per year, and in the group of patients 1.6% per year, again similar to controls. Thus, the declines of TT and of DHEAS with age in female patients with HD are not different from that of healthy subjects.

DISCUSSION

Total testosterone, cortisol, and DHEAS levels of female patients with HD and of female subjects at risk for the disease, do not differ significantly from those of healthy females. The rate of decline with age of TT and of DHEAS in female HD patients was similar to that of healthy women. These data suggest that the HPA axis is normally functioning in female patients with HD, as well as in subjects at risk of developing the disease.

There was no association of TT or DHEAS levels with the presence of dementia in the patients' symptomatology. This is in line with the study of Hoskin *et al.* [17], in which the TT and DHEA levels of women over the age of 65 with Alzheimer's disease did not differ from the levels of non-demented controls. DHEAS levels were also not associated to the presence of dementia in older male and female subjects [9], or to cognitive performance in neuropsychological tests of men and women over 65 years [8]. Yaffe *et al.* [23], in a study of cognitive functions in a large number of women aged 65 years and older, conclude that "serum DHEAS is not a sensitive predictor of cognitive performance or decline on a selected neuropsychological battery in elderly community women; however, nondetectable levels may be associated with depression". The findings of the present study in patients with HD, are close to that conclusion, i.e. that DHEAS levels are not connected to cognitive function but to depressive symptomatology. To the same conclusion regarding females, come Berr *et al.* [24], after studying for 4 years a large number of subjects over 65 years of age.

The levels of TT and of DHEAS were found to be lower in patients with depression in their symptomatology. In the study of Barrett-Connor *et al.* [15] in women aged 50 to 90 years, depressive mood was associated to the levels of DHEAS, but not to testosterone, and a subset of women with definite depression had lower levels compared with nondepressed, age-matched women. The positive effect on mood after administration of DHEA, found in several studies, adds further evidence for this association. Treatment of midlife-dysthymia with DHEA, produced a clearly positive effect on mood in men and women aged 45 to 63 years [25]. The drug had no effect on cognitive functions, evaluated by neuropsychological tests for memory, spatial and verbal ability, or attention and concentration.

The mechanisms by which DHEAS may interfere with depressive symptomatology and the sense of well-being are poorly understood. It is probable that DHEAS interferes with other hormones or modulates neurotransmitter actions. DHEAS is a neurosteroid, i.e. a steroid that can modulate neuronal activity. Actually, it is the first substance that was named neurosteroid when the term was introduced by Baulieu [26]. DHEAS is a potent allosteric antagonist of the GABA(A) receptor [27], and this is of special interest for HD, where GABAergic neuronal loss is a part of the degeneration process [28].

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