Adrenal steroids in adrenomyeloneuropathy
Dehydroepiandrosterone sulfate, androstenedione and 17α-hydroxyprogesterone

Abstract Adrenoleukodystrophy (ALD) and its adult variant adrenomyeloneuropathy (AMN) are X-linked diseases associated with a deficiency in the peroxisomal degradation of saturated very long chain fatty acids (VLCFAs) resulting in an accumulation of VLCFAs in the central and peripheral myelin, the adrenal cortex and the testis.

Adrenal insufficiency with clinical hypocortisolism occurs in approximately two thirds of the patients with AMN. We studied the circulating adrenal hormones 17α-hydroxyprogesterone (17α-OHP), androstenedione and dehydroepiandrosterone sulphate (DHEAS) in 63 male AMN patients (age 17–65 years) and the DHEAS serum levels in 95 healthy male controls (age 30–65 years). 34 of the patients presented with the phenotype of only spinal cord and peripheral nerve disability without hypocortisolism, 29 of the patients presented with the phenotype of either additional hypocortisolism or Addison’s syndrome only. Normal 17α-OHP concentrations were found in all patients with no significant difference between patients without and with hypocortisolism (6.07 ± 0.61 nmol/l and 4.76 ± 0.37 nmol/l). Androstenedione concentration was significantly (p < 0.01) lower in patients with hypocortisolism (2.99 ± 0.65 pmol/l versus 5.71 ± 0.68 pmol/l). As serum levels of DHEAS are age-dependent we divided the two groups into two subgroups each (subgroup one: age 17–40 years, subgroup two: age 41–65 years). The DHEAS concentration of patients without and with hypocortisolism was significantly (p < 0.01) lower in both subgroups (1. 4.35 ± 0.84 μmol/l, n = 15, 2. 15 ± 0.28 μmol/l, n = 19; 1. 1.90 ± 0.57 μmol/l, n = 21, 2. 0.96 ± 0.29 μmol/l, n = 8) compared to controls (1. 9.0 ± 0.96 μmol/l; 2. 5.21 ± 0.25 μmol/l). In conclusion, androstenedione and DHEAS serum concentrations are subnormal in all AMN patients and may therefore serve as sensitive markers of the adrenal function in adrenomyeloneuropathy.

Key words AMN · DHEAS · androstenedione · 17α-hydroxyprogesterone · hypocortisolism

Introduction

Adrenoleukodystrophy (ALD; McKusick 300100) is an X-linked neurodegenerative disorder. This most common peroxisomal disorder is characterised biochemically by a defect in the degradation of saturated very long chain fatty acids (VLCFAs). It results in abnormal accumulation of VLCFAs in plasma and various tissues, predominantly in myelin, adrenal cortex and testis [23, 25, 33]. The disease shows great variation in clinical phenotype. The most common and severe phenotype is cerebral childhood ALD. Progressive inflammatory demyelination of the brain white matter leads to a vegetative state and death usually within two to four years from first onset of symptoms. The adult cerebral variants are less common, starting with behavioural abnormalities,
dementia or schizophrenia in addition to neurological symptoms. Adrenomyeloneuropathy (AMN) represents a milder form of ALD which progresses more slowly and which involves mainly the spinal cord and the peripheral nerves. In the second or third decade of life, male patients with AMN present with symptoms of peripheral neuropathy and progressive spastic paraparesis. Almost two thirds of the patients with ALD/AMN also show varying degrees of adrenal insufficiency. Isolated adrenal insufficiency ('Addison-only' phenotype) can be an early sign of childhood ALD or AMN presented before the onset of neurological symptoms [10]. A small number of patients have neither neurological nor endocrinological deficits (asymptomatic phenotype) [31] but are at risk of developing either of the symptomatic phenotypes later on in life.

Adrenal insufficiency in affected patients is confirmed by the presence of an impaired cortisol secretion and increased ACTH concentration. Usually, results of the conventional ACTH stimulation tests are below normal levels [10]. In addition, elevated ACTH concentrations may identify patients with limited adrenocortical reserve that would not be detected by ACTH stimulation alone [9]. Low dehydroepiandrosterone sulfate (DHEAS) levels in ALD patients have previously been described [4, 5].

We measured the steroid hormones dehydroepiandrosterone sulfate (DHEAS), androstenedione and 17α-hydroxyprogesterone to detect a possible second sensitive marker of adrenal insufficiency.

Materials and methods

■ Patients

We studied 63 male AMN patients. All patients had normal brain MRI examinations (‘pure’ AMN phenotype). Of these, 34 patients (mean age 42.3 ± 1.9 years, range 23–65; duration of illness 13.2 ± 1.4 years) presented with the phenotype of only spinal cord and peripheral nerve disability without hypocortisolism. The remaining 29 patients (mean age 35.5 ± 2.2 years, range 17–65, duration of illness 13.3 ± 1.5 years) presented with the phenotype of spinal cord and peripheral nerve disability as well as additional hypocortisolism (n = 24), or only the Addison phenotype (n = 5). Adrenal function was considered to be normal when either the basal serum cortisol concentration or the cortisol concentration after corticotropin stimulation test was at least 550 nmol/l. Corticotropin (0.25 mg, Synachten, Novartis, Nuremberg, Germany) was given intravenously before 10 am, and serum cortisol was measured before and 60 minutes after the injection.

The patients with primary adrenal hypocortisolism received replacement therapy with 15 to 25 mg hydrocortisone per day. Additionally, 19 of these patients received replacement therapy with mineralocorticoids at 0.1 mg/day. Also, 26 of them received dietary therapy of 60 ml/day Lorenzo’s oil, whereas 26 patients of the group without hypocortisolism received Lorenzo’s oil (60 ml/day) only.

Serum DHEAS levels were measured in 95 healthy male controls (mean age 49.8 ± 0.8 years, range 30–65).

■ Methods

Serum was assayed for cortisol by fluorescence polarisation immunoassay (TDx, Abbott, Wiesbaden, Germany). The assay sensitivity was 18 nmol/l, intra- and interassay coefficients of variation (CV) were 2.6% and 4%, respectively (mean 428 nmol/l, n = 10). Serum was assayed for dehydroepiandrosterone sulfatel (DHEAS) and 17α-hydroxyprogesterone (17α-OHP) by radioimmunoassay (RIA) (DPC Biermann, Bad Nauheim, Germany). The DHEAS assay sensitivity was 0.03 µmol/l, intra- and interassay CV were 4.4% (mean 5.2 µmol/l, n = 20) and 6.3% (mean 5.6 µmol/l, n = 20), respectively. The 17α-OHP assay sensitivity was 0.21 nmol/l, intra- and interassay CV were 5% and 5% (mean 6.1 nmol/l, n = 20), respectively. Serum was assayed for androstenedione by RIA (DSL, Webster, Texas, USA). The assay sensitivity was 0.07 pmol/l, the intra- and interassay CV were 2.7% (mean 7.8 pmol/l, n = 10) and 4.8% (mean 7.3 pmol/l, n = 10), respectively.

■ Statistics

The results were expressed as the mean ± standard error of the mean (SEM). Undetectable hormone concentrations were expressed as the detection limit for statistical purposes. The Wilcoxon-Mann-Whitney U-test was used for comparison of the groups. Correlations were performed using Pearson’s rank correlation. A probability value of less than 0.05 was regarded as statistically significant.

Results

The AMN patients with only spinal cord and peripheral nerve disability without hypocortisolism showed a mean 17α-OHP concentration of 6.07 ± 0.61 nmol/l (n = 33) (Table 1). The mean 17α-OHP concentration of the AMN patients with hypocortisolism was 4.76 ± 0.37 nmol/l (n = 28). There was no significant difference between the two groups. All 17α-OHP values were within the reference range (1.2–9.9 nmol/l).

The mean androstenedione concentration in the group without hypocortisolism was 5.71 ± 0.68 pmol/l (n = 34), and, with the exception of three values, all values were within the normal range (2.0–9.1 pmol/l) (Table 1). The androstenedione concentration in the group with hypocortisolism was significantly (p < 0.01) lower, 2.99 ± 0.65 pmol/l (n = 28). Sixteen patients had values below the reference range.

The serum concentration of DHEAS is age depen-