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SHORT COMMUNICATION

A NEW DEFECT IN THE PERIPHERAL CONVERSION OF CORTISONE TO CORTISOL

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Summary—A steroid disorder is described in two sisters, aged 13 and 17 years, in which the metabolism of cortisol results almost exclusively in urinary excretion of tetrahydro-cortisone (11-keto) derivatives. The evidence implies the existence of a deficiency in the peripheral enzymatic conversion of cortisone to cortisol.

Application of techniques associated with capillary gas chromatographic analysis of neutral urinary steroids has allowed the unambiguous documentation of numerous steroid disorders [1,2]. Recently, several groups, including our own, independently found evidence in several infants of a basic deficiency in the transformation of cortisol to cortisone [3]. In this communication we describe for two sisters of caucasian parents, a previously unreported steroid deficiency associated with the inability of cortisone to be reduced to cortisol.

The older sister (17 yr) presented at the clinic with dysmenorrhea and extensive hirsutism. She was a thin healthy young woman of height 154 cm, weight 49 kg and normal secondary sexual development. Blood pressure was 110/70 and there was no striae or signs of Cushings Syndrome. She had a history of acne vulgaris since the age of 7 yr, increasing hirsutism from 12 yr and menarche at 15 yr followed by 1 year of regular periods. Abdominal C-T scan, after intravenous contrast injection, showed no evidence of enlargement of either adrenals or ovaries. All laboratory tests of thyroid function (free thyroxine, total T3, TSH, free thyroxine index) gave values within the accepted reference ranges. Plasma levels of DHEA-S (30 μM, Normal Range (NR) 3–11) and testosterone (6.3 nM, NR 0.5–3.5) were markedly elevated. The urinary steroid profile (see Fig. 1) was atypical with respect to the pattern of cortisol and androgen metabolites, when compared to that of a normal female (Fig. 2). Subsequent investigation of her immediate family (father, mother and sister [13 yr]) revealed that the sister had a similar urinary steroid profile (cf. Fig. 1).

Abbreviations: THE, tetrahydrocortisone = 3α,17β,21-trihydroxy-5β-pregnane-11,20-dione. THF, tetrahydrocortisol = 3α,11β,17β,21-tetrahydroxy-5β-pregnan-20-one. allo-THF = 3α,11β,17β,21-tetrahydroxy-5α-pregnan-20-one. Pdiol = 5β-pregnane-3α,20α-diol. 11-OH-A = 3α,11β-dihydroxy-5α-androstan-17-one.

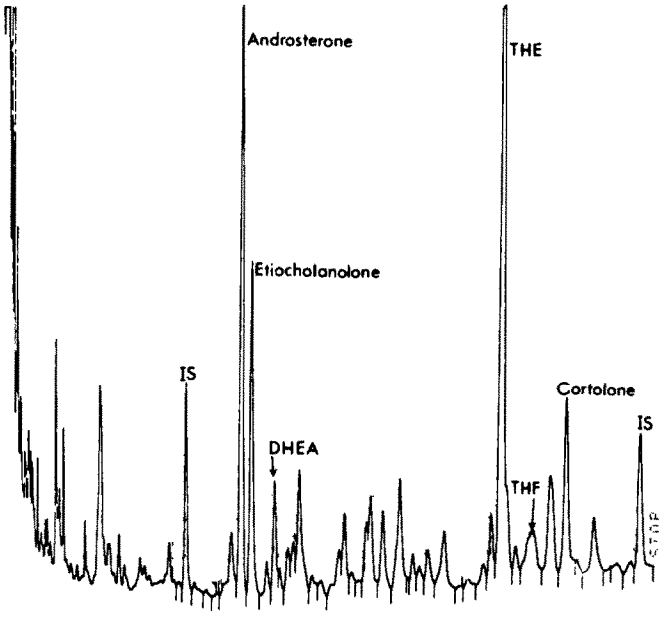

Fig. 1. Urinary steroid profile for suspected cortisone to cortisol defect. Steroid chromatographed as methyloxime-TMS derivatives on 15 m × 0.3 mm OV-101 vitreous silica capillary column. IS = internal standard, *n*-tetracosane and *n*-dotriacontane respectively.

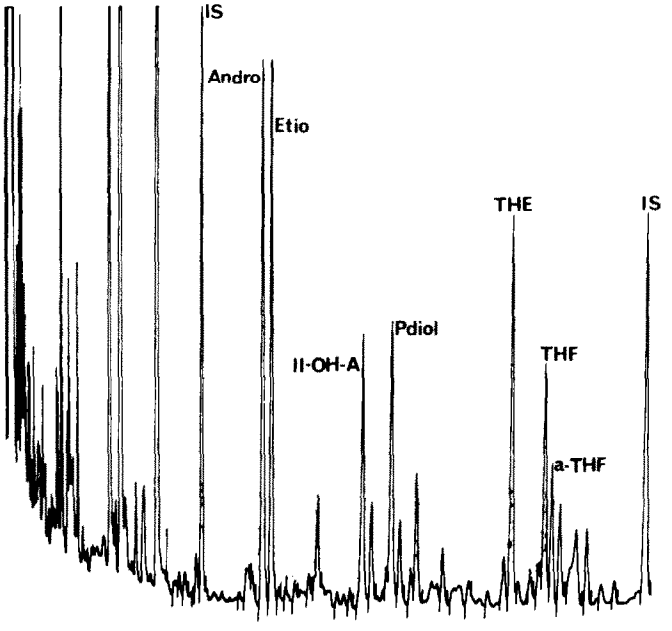

Fig. 2. Urinary steroid profile for a normal 19 yr old female. Conditions as for Fig. 1.

The younger sister did not present for a complete clinical evaluation, but at the time plasma and urine samples were taken, was found to be slightly hirsute. She had only recently completed menarche.

The steroid pattern shown in Fig. 1 is abnormal due to the virtual absence of corticoid 11 beta-hydroxy metabolites, such as THF and allo-THF, in comparison to the levels of 11-oxo metabolites (THE and cortolone). The ratio of etiocholanolone to androsterone is also low (0.4, NR 0.5–2.3). The identity of all steroids was unambiguously confirmed by gas chromatography–mass spectrometric analysis.

Adrenal suppression of the elder sister could not be achieved with either oral cortisone acetate (100 mg) or hydrocortisone (100 mg). Both the latter glucocorticoids, subsequent to metabolism, were excreted in the urine almost exclusively as THE. Complete adrenal suppression however, could be obtained using dexamethasone (2 mg). It is noteworthy that the latter dose of dexamethasone is approx 50% that administered for the natural glucocorticoids on an equivalence basis [4]. The suppression results provide confirmatory evidence for the presence of an enzyme deficiency as opposed to a steroid secreting tumour or adenoma.

The evidence for a specific defect in the 11-oxidoreductase system may be summarised as follows. Firstly, a defect in cortisol production can be discounted since the adrenal secretion of cortisone is negligible and it is almost entirely formed by 11-oxidation of cortisol [5]. Furthermore, high pressure liquid chromatographic analysis of plasma confirmed the presence of cortisol [6]. The virtual absence of cortisol metabolites (11-beta hydroxy) in urine and the marked preference to metabolize oral doses of either cortisone acetate or hydrocortisone to THE, highlights a major abnormality in the normal plasma interconversion of cortisol and cortisone. In previous investigations of patients on high dose natural glucocorticoids, THF, not THE, was the major urinary metabolite [2]. The effectiveness of the synthetic corticoid, dexamethasone, reflects its alternate mode of metabolism which does not involve the 11-position [7].

In normal subjects the metabolic clearance rate is significantly greater for cortisone than cortisol, however the transfer constant favours the conversion of cortisone to cortisol [5]. Formation of cortisone represents the main deactivation route of plasma cortisol. Aberrations in the cortisone to cortisol step would require enhanced adrenal production of cortisol and increased clearance of cortisone to maintain the equilibrium state. This in turn must also effect the subsequent metabolism of cortisol, which from the results appears to be mainly converted to cortisone, with little metabolism to tetrahydro derivatives. Previous workers have in fact suggested that the liver metabolism of cortisone may be in a separate compartment from which THE is the almost exclusive product [5]. The same authors note that there is also little inter-conversion between THE and THF.

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