Congenital adrenal hyperplasia
due to partial 21-hydroxylase deficiency.
A study of five cases

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Abstract. Five women with post pubertal hirsutism due to a partial 21-hydroxylase deficiency were studied. These patients had no abnormalities of the external genitalia. They were compared to 3 adult women with a complete defect in 21-hydroxylase. The diagnosis of 21-hydroxylase deficiency was substantiated by the dramatic increase in 17-hydroxyprogesterone (17-OHP) after im injection of 250 µg synthetic ACTH (22 ± 12 nmol/l to 349 ± 153 nmol/l). However, in adult women with 21-hydroxylase deficiency recognized at birth and presenting abnormalities of the external genitalia, plasma 17-OHP was elevated in basal conditions (512 ± 106 nmol/l) and only slightly increased after ACTH administration (657 ± 133 nmol/l). Plasma cortisol levels determined at 08.00 h were lower than normal in both groups but only slightly in groups with partial 21-hydroxylase deficiency. After ACTH stimulation, plasma cortisol levels remained lower than normal in all patients but with a noticeable increase in patients with partial defect. The differences noted between precocious and delayed onset virilization gave an indication of the importance of the enzyme defect. Plasma testosterone (T) and androstenedione (Δ4) levels were elevated both in basal conditions and after ACTH administration. However, in patients with delayed onset of hirsutism most circulating T seems to originate from peripheral conversion of Δ4 to T. Plasma ACTH values were strongly elevated in patients with a complete defect in 21-hydroxylase (260 ± 50 pg/ml) but normal in patients with partial deficiency (< 40 pg/ml).

In vitro testosterone 5α-reductase activity was determined in pubic skin homogenates from 4 patients with partial 21-hydroxylase deficiency. The amount of dihydrotestosterone + androstanediols formed from incubated [3H]testosterone was in the normal range for women. Virilization of patients with partial 21-hydroxylase deficiency therefore seems to be essentially due to an increase in active androgen production and not to exaggerated skin ‘utilization’ of pre-androgens as observed in idiopathic hirsutism.

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is generally diagnosed at birth in girls, and most patients do present, even in the absence of clinical adrenal insufficiency, some abnormalities of the external genitalia. However, virilization due to the delayed form of this congenital syndrome has been described in childhood, after puberty or during adulthood (Decourt et al. 1957; Brooks et al. 1960; Cara & Gardner 1960; Lipsett & Riter 1961; Molinatti et al. 1964; Mahesh et al. 1968; Riddick & Hammond 1975; Rosenwaks et al. 1979; Bricaire et al. 1979).

In this report, 5 cases of acquired hirsutism without any other sign of virilization are described.
The hormonal features observed in these patients were characteristic of CAH due to incomplete 21-hydroxylase deficiency. They are compared with 3 cases of complete deficiency.

Materials and Methods

The 5 women studied were respectively 20, 23, 25, 26 and 35 years old. Hirsutism developed after a normal puberty. It was moderate or severe but without male-type muscle increase or citoromegaly. Clinical history did not show salt loss syndrome at birth. No family history of salt loss or hirsutism was noted. Menstrual cycles were ovulatory in all 5 cases. Two of the patients had had normal pregnancies prior to their first clinical observations. Gynaecological examination was normal. No enlarged ovaries were found upon pelvic examination. In summary these patients were often considered as having idiopathic hirsutism.

The 3 patients with the complete form of 21-hydroxylase deficiency had no salt loss syndrome but signs of virilization of the external genitalia at birth and the diagnosis had been made during the first years of life.

They were studied after interrupting substitutive cortisol treatment for 2 months. At this time, they were 25, 30 and 33 years old.

Plasma cortisol, 17-hydroxyprogesterone, (17-OHP), testosterone (T), androstenedione (Δ4), dehydroepiandrosterone sulphate (DHA-S) and urinary androstane-3α, 17β-diol (Adiol) were determined by radioimmunoassay (RIA) as previously described (Kuttenn et al. 1977; Wright et al. 1978; Pham-Huu-Trung et al. 1978). These determinations were performed during the follicular phase in basal conditions and 1 h after im administration of 0.25 mg synthetic ACTH: β 1-24 tetracosactide (Synacthen®, Giba). Blood samples were always collected at 8 a.m. Plasma ACTH was assayed by RIA (Proeschel et al. 1974).

In vitro, skin specimens of pubic origin were obtained from biopsy under local anaesthesia in 4 patients with partial 21-hydroxylase deficiency and the 3 patients with complete defect. T 5α-reductase activity was measured in a 100 mg sample after removal of subcutaneous fat. Homogenization, incubation and identification of recovered radioactive steroids were performed according to usual procedure (Kuttenn et al. 1977). Conversion of [3H]T into [3H]DHT + 3α-5β-androstenediols was expressed in fmol/mg of skin.

![Graphs showing plasma levels of cortisol, 17-hydroxyprogesterone, testosterone, androstenedione, and dehydroepiandrosterone sulphate before and after ACTH injection.](image)

Plasma levels of cortisol (F), 17-hydroxyprogesterone (17 OHP), testosterone (T), Δ4-androstenedione (Δ4) and dehydroepiandrosterone sulphate (DHA-S) before and after im synthetic ACTH injection, in patients with complete (●) and partial (○) adrenal 21-hydroxylase deficiency. (Normal range for women, mean ± 2 SEM: []).
patients with partial 21-hydroxylase deficiency (<40 pg/ml) whereas in the 3 patients with complete deficiency the value was very high (260 ± 50 pg/ml).

As regards plasma androgens, DHA-S level was normal in both groups in basal conditions as well as after ACTH stimulation. Control values of plasma Δ4 were elevated in both forms of enzyme defect. However in partial defect Δ4 mean value (13.2 ± 4.2 nmol/l) was half that of complete defect (25.1 ± 5.2 nmol/l).

After ACTH, the mean plasma Δ4 level was very similar in the 2 groups of patients (32.1 ± 4.2 and 35.9 ± 5.2 nmol/l respectively). Plasma T was only slightly elevated in patients with partial enzyme defect (2.7 ± 1.4 nmol/l) and did not increase significantly after ACTH administration (5.5 ± 2.4 nmol/l). By contrast, in patients with complete defect, basal plasma T was very high (12.1 ± 5.2 nmol/l) and did not increase significantly after ACTH (14.5 ± 4.1 nmol/l).

Plasma DHT was elevated in patients with the complete enzymatic defect (2.33 ± 0.34 nmol/l) but not significantly higher than normal in patients with partial defect (1.54 ± 0.41 nmol/l) while urinary Adiol excretion was frankly elevated in the 2 groups (644 ± 143 and 1074 ± 51 µmol/24 h respectively).

### Results

**Plasma and urinary hormones**

Measurement of plasma and urinary hormones are given in Figs. 1 and 2 and Table 1. Mean plasma 17-OHP ± se in patients with partial 21-hydroxylase deficiency was only slightly elevated in basal condition (22 ± 12 nmol/l). However after ACTH injection there was a striking and significant increment compared to normal (349 ± 153 nmol/l; P < 0.001). Mean plasma cortisol at 8 a.m. was normal or low (292 ± 179 nmol/l) and not significantly different from values observed in the 3 patients with complete 21-hydroxylase deficiency (193 ± 88 nmol/l). A slight, but still subnormal, increase was observed after ACTH administration, whereas no response at all was noted in the patients with complete enzyme defect (Fig. 1).

Plasma ACTH was in normal range in the 5

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Plasma ACTH (pg/ml)</th>
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<tr>
<td>Normal</td>
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<tr>
<td>21-Hydroxylase</td>
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</tr>
<tr>
<td>Complete defect</td>
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<td>310</td>
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<td>&lt; 2</td>
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### Table 1.

Plasma ACTH levels in normal subjects and patients with complete (n = 3) and partial (n = 5) 21-hydroxylase deficiency.
In vitro determination (Fig. 2)

Testosterone 5α-reductase activity was found normal or subnormal in the four cases studied with partial defect: 23, 38, 40 and 45 fmol/mg skin, since the normal range for women is from 30 to 70 fmol/mg skin. But 5α-reductase activity was always higher than normal in the 3 patients with complete defect: 80, 115 and 118 fmol/mg skin.

Discussion

The milder forms of 21-hydroxylase deficiency have been described by different investigators. However, in most of them, the diagnosis was based on urinary determinations of 17-ketosteroids and pregnanetriol only; except in 3 reports (Leichter & Jacobs 1976; Gournelen et al. 1979; Bricaire et al. 1979), there was no extensive appreciation of plasma androgens and 17-hydroxyprogesterone.

The 5 cases reported in this paper were selected from an extensive investigation of 250 women who consulted our department for acquired hirsutism between 1975 and 1979. This small number of patients with 21-hydroxylase deficiency gives an idea of the relative rarity of this syndrome.

When the 5 patients studied were compared with others with complete 21-hydroxylase defect, it appeared obvious that the enzymatic block was only partial. In these 5 patients, in basal conditions, plasma 17-OHP was only slightly higher than normal, but showed a dramatic increase after ACTH administration. By contrast, in patients with complete enzymatic defect, 17-OHP was very high in basal conditions, and showed no increase after ACTH stimulation.

These observations correlate with the values of plasma ACTH obtained in the 2 groups of patients. Plasma ACTH is markedly high in the complete form of 21-hydroxylase defect, whereas the normal values of plasma ACTH observed in patients with acquired virilization indicate that, at least in basal conditions, without any stress or physical or psychological stimulation of ACTH production, the merely partial defect in 17-hydroxylase permits sufficient cortisol production to exert a normal negative feedback on ACTH production (Pham-Huu-Trung et al. 1978).

Hirsutism in patients with partial defect in 21-hydroxylase seems to be induced by the increase of Δ4 production. Deficiency of the 17-hydroxylase enzyme leads to an increase in 17-OHP biosynthesis; 17-OHP is metabolized through alternate pathways to either pregnanetriol (Fukushima et al. 1961) or Δ4 (Rivarola et al. 1967); Δ4 is then converted to T (Horton & Frasier 1967). The comparison of plasma Δ4 and T suggests that in patients with partial enzyme defect most of T originates from the peripheral conversion of Δ4 and not from direct secretion by adrenals. However, in patients with a complete defect the high levels of plasma T compared with those of plasma Δ4 imply a direct secretion by the adrenals, as noted by other investigators (Burger et al. 1964).

5α-reductase activity differs according to the type of 21-hydroxylase deficiency. It is very elevated in patients with the complete form of the syndrome. This may be due to the increased secretion of T by the adrenals which may stimulate 5α-reductase activity in the skin as observed in man at puberty (Mauvais-Jarvis 1977). On the other hand, in patients with only a partial defect 5α-reductase activity is in the range of normal women. It is also far lower than in idiopathic hirsutism (Kuttenn et al. 1977). In patients with idiopathic hirsutism plasma T and Δ4 are indeed only slightly elevated; the high level of T 5α-reductase activity in pubic skin and the elevated urinary excretion of Adiol suggest an exaggerated ‘utilization’ of androgens by skin (Kuttenn et al. 1977; Wright et al. 1978). By contrast in patients with partial 21-hydroxylase deficiency the major factor which seems to be responsible of virilization is the elevated production of Δ4. In other words the increased Adiol excretion observed in these patients reflects more the elevated production of Δ4, than the increased transformation of Δ4 to T, DHT and diols in the skin.

In a recent report, Leichter & Jacobs (1976) suspected a partial androgen resistance in a 22 year old woman with 21-hydroxylase deficiency but minimal clinical evidence of virilization. Since hirsutism depends on androgen production and/or skin androgen sensitivity, observation of a normal or low 5α-reductase activity in pubic skin of patients with partial 21-hydroxylase deficiency is interesting to consider. Recent reports from our laboratory have suggested that hair growth in secondary sex differentiation territories was mediated by the rate of 5α-reductase activity present at puberty (Mauvais-Jarvis 1977). In addition, 5α-reductase activity in pubic skin seems to be a good marker of androgen responsiveness (Kuttenn et al. 1979).
1979). On the other hand, a low enzyme activity may be responsible for androgen insensitivity. Thus genetic differences in 5α-reductase activity in sexual skin might explain variable responses of target cells to the same androgenic stimulus.

References

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