Long Term Follow-Up of a 46,XY Phenotypic Girl with 17α-Hydroxylase Deficiency Treated with Alternate-Day Dexamethasone

MARI SATOH, SUSUMU YOKOYA*, REIKO HASHIGUCHI, AND NORIYUKI KATSUMATA**

Abstract. We report an 18-year-old 46,XY phenotypic girl who has been on alternate-day dexamethasone therapy for 10 years. The patient was seen at our hospital for right-sided inguinal hernia at the age of 4 years. Biopsy of the herniated gonad showed testicular tissue, and the karyotype of the peripheral lymphocytes was 46,XY. The diagnosis of 17α-hydroxylase deficiency was established by the evaluation of adrenal steroidogenesis at the age of 6.1 years when hypertension was clearly recognized, and was confirmed later by the gene analysis of CYP17 which disclosed a compound heterozygote. The growth rate was suppressed during the initial treatment with daily administration of 0.25-0.5 mg dexamethasone. Switching to alternate-day regimen of dexamethasone 0.5 mg/dose improved height velocity. Subsequent addition of low-dose estrogen therapy induced pubertal growth spurt. The blood pressure and adrenal hormone levels remained almost within the normal range throughout the course. Adrenal function was evaluated at the age of 15 years. Plasma ACTH and corticosterone levels were high only just before the next administration, when the plasma dexamethasone concentration should be at the nadir. Since corticosterone possesses glucocorticoid activity and can work as a glucocorticoid reserve, it is assumed that this mode of dexamethasone administration can be a safe treatment for this disorder. We conclude that the patient with childhood 17α-hydroxylase deficiency can be safely and effectively treated with alternate-day dexamethasone without interfering with linear growth.

Key words: 17α-Hydroxylase deficiency, Dexamethasone, Growth, Final height, 46,XY

17α-HYDROXYLASE deficiency is one of the rare forms of congenital adrenal hyperplasia. It is caused by a deficiency of p450 17α (CYP17) which catalyzes both 17α-hydroxylase and 17,20-lyase reactions. The gene for this enzyme is located on chromosome 10 [1] and expressed both in the gonad and the adrenal cortex. Since the first report by Biglieri et al. [2], more than 120 cases of this disorder have been reported [3]. Since most cases are found after adolescence because of sexual infantilism and/or hypertension, we have limited knowledge regarding the adequate treatment and its influence on growth during childhood and adolescence. Moreover, longitudinal growth patterns of children with 17α-hydroxylase deficiency have not been reported whether with or without treatment. We report an 18-year-old phenotypic girl with the karyotype of 46,XY who has been treated on alternate-day dexamethasone therapy for 10 years.
**Case Report**

The patient was born to non-consanguineous parents after a 41 week uneventful gestational period and reared as a girl. The body weight was 3050 g (−0.36 SD as a girl and −0.46 SD as a boy) at birth. No particular family history was recognized. The father’s height was 164 cm and the mother’s 157 cm, the patient’s target height was 169 cm for boys and 156 cm for girls. The younger sister had a normal menstrual cycle. When the patient developed Kawasaki disease at the age of 1.3 years, the blood pressure was found to be high (124–88/94–50 mmHg) and serum K levels were constantly low (2.6–3.5 mEq/l). These findings, however, did not lead us to the diagnosis of the underlying disease. There was no episode of hypoglycemia or other symptoms suggesting adrenal insufficiency during infancy and childhood.

The patient was seen at the Department of Surgery, Toho University School of Medicine, for right-sided inguinal hernia at the age of 4 years. Biopsy of the herniated gonad showed testicular tissue and it was therefore totally removed. The karyotype found in the peripheral lymphocytes was 46,XY. The presumptive diagnosis at that time was testicular feminization. Since hypertension became more evident (138–88/94–50 mmHg), detailed endocrinological examination was performed at the age of 6.1 years. The diagnosis of 17α-hydroxylase deficiency was made because of the reduced levels of 17-hydroxysteroids, 17-ketosteroids and plasma renin activity (PRA) and high levels of 17-deoxysteroids and ACTH (Table 1). Furthermore, a noticeable increase in basal and peak LH and FSH concentrations after stimulation with GnRH was observed (16.4 to 91.4 IU/l and 48.9 to 172 IU/l, respectively). After these studies, the left inguinal gonad was also removed. The external genitalia were phenotypically female but looked immature. The vagina ended at 2 cm in depth.

The treatment was initiated with daily administration of 25 mg of hydrocortisone (29.4 mg/m²) at the age of 6.3 years. Although the dose was increased to 35 mg/day (41.2 mg/m²), blood pressure remained high. Therefore, treatment with daily dexamethasone at a dose of 0.5 mg (0.56 mg/m²) was started at the age of 6.4 years, and was followed by normalization of blood pressure. A decrease in the dose of dexamethasone to 0.25 mg/day (0.28 mg/m²) was effective in controlling blood pressure and adrenal function to within the normal ranges. Growth retardation was observed after the start of treatment with daily dexamethasone as shown in Fig. 1. Changes in growth were plotted on the Japanese standard for girls (Fig. 1a) and for boys (Fig. 1b). In order to restore growth velocity, alternate-day administration of dexamethasone was attempted at the age of 7.2 years with an initial dose of 0.25 mg (0.28 mg/m²) followed by an increase to 0.375 mg (0.39 mg/m²). Since this treatment resulted in increased plasma levels of deoxycorticosterone (DOC) and corticosterone and decreased PRA, the dose was increased to 0.5 mg (0.52 mg/m²) at the age of 8.1 years. Since this change the patient has had normal blood pressure and adrenal function, despite a gradual decrease in the relative dexamethasone dose to 0.32 mg/m². Height velocity dramatically improved after the introduction of alternate-day therapy. Although height velocity remained normal during the first two years of alternate-day therapy, the growth rate was again reduced at the age of 9 years. The body mass index was 16.5–18.9 and obesity did not occur during the course of dexamethasone treatment. The bone age, evaluated with Tanner-Whitehouse 2 RUS scoring system standardized for either Japanese girls or boys [4], was retarded. Estrogen replacement therapy was started with 3.5 μg/day of conjugated estrogens at the age of 11.1 years. Thereafter, the estrogen dose was increased.

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**Table 1.** Hormonal levels before and after intravenous administration of 0.25 mg ACTH at the age of 6.1 years

<table>
<thead>
<tr>
<th>Time</th>
<th>Progesterone (ng/ml)</th>
<th>DOC (ng/ml)</th>
<th>Corticosterone (ng/ml)</th>
<th>Aldosterone (pg/ml)</th>
<th>17α-hydroxyprogesterone (ng/ml)</th>
<th>Cortisol (μg/dl)</th>
<th>ACTH (pg/ml)</th>
<th>Δ4-Androstenedione (ng/ml)</th>
<th>Testosterone (ng/ml)</th>
<th>PRA (ng/ml/h)</th>
<th>DOC, deoxycorticosterone; PRA, plasma renin activity; ND, non-detectable.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.42</td>
<td>6.04</td>
<td>262</td>
<td>305</td>
<td>0.272</td>
<td>3.1</td>
<td>60</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>3.67</td>
<td>7.20</td>
<td>496</td>
<td>308</td>
<td>0.257</td>
<td>3.5</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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The treatment was initiated with daily administration of 25 mg of hydrocortisone (29.4 mg/m²) at the age of 6.3 years. Although the dose was increased to 35 mg/day (41.2 mg/m²), blood pressure remained high. Therefore, treatment with daily dexamethasone at a dose of 0.5 mg (0.56 mg/m²) was started at the age of 6.4 years, and was followed by normalization of blood pressure. A decrease in the dose of dexamethasone to 0.25 mg/day (0.28 mg/m²) was effective in controlling blood pressure and adrenal function to within the normal ranges. Growth retardation was observed after the start of treatment with daily dexamethasone as shown in Fig. 1. Changes in growth were plotted on the Japanese standard for girls (Fig. 1a) and for boys (Fig. 1b). In order to restore growth velocity, alternate-day administration of dexamethasone was attempted at the age of 7.2 years with an initial dose of 0.25 mg (0.28 mg/m²) followed by an increase to 0.375 mg (0.39 mg/m²). Since this treatment resulted in increased plasma levels of deoxycorticosterone (DOC) and corticosterone and decreased PRA, the dose was increased to 0.5 mg (0.52 mg/m²) at the age of 8.1 years. Since this change the patient has had normal blood pressure and adrenal function, despite a gradual decrease in the relative dexamethasone dose to 0.32 mg/m². Height velocity dramatically improved after the introduction of alternate-day therapy. Although height velocity remained normal during the first two years of alternate-day therapy, the growth rate was again reduced at the age of 9 years. The body mass index was 16.5–18.9 and obesity did not occur during the course of dexamethasone treatment. The bone age, evaluated with Tanner-Whitehouse 2 RUS scoring system standardized for either Japanese girls or boys [4], was retarded. Estrogen replacement therapy was started with 3.5 μg/day of conjugated estrogens at the age of 11.1 years. Thereafter, the estrogen dose was increased.
gradually to 1.25 mg/day as shown in Fig. 1 and breast development had reached Tanner stage 4 by the age of 15 years. The growth rate significantly increased after estrogen was increased to 62.5 µg/day. At an estrogen dose of 625 µg the height velocity reached the peak value of 7.5 cm/year which was close to the mean peak height velocity for Japanese girls. Stanozolol (0.5 mg/day) was introduced at the age of 14.8 years. After the dose was increased to 1.0 mg/day, growth of pubic hair appeared, but no other androgen effects were evident. The height became 166.6 cm at 18 years of age and the patient is still gradually growing and approaching the target height as a boy which is 169 cm (Fig. 1).

At the age of 15.9 years, the diurnal variation in adrenal hormone levels was studied for two consecutive days to evaluate the effect of alternate-day dexamethasone therapy (0.32 mg/m²). As shown in Table 2, plasma ACTH and corticosterone increased only before the next dexamethasone administration, when the plasma dexamethasone concentration should be at its nadir. Plasma DOC and PRA remained unchanged.

Analysis of the CYP17 gene revealed a compound heterozygote. One mutation was a single base deletion (CTT to CT) at codon 247 in exon 4 which resulted in premature stop (TGA) at codon 267 and the other was a missense mutation (CAC to CTC) at codon 373 causing His 373 Leu substitution in exon 6.

Discussion

Diagnosis of 17α-hydroxylase deficiency is usually established after adolescence, because the clues for the diagnosis in most cases are lack of

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Fig. 1. Changes in height (closed circles), growth velocity and bone age (open circles) plotted on female (1a) and male (1b) standard for Japanese.
pubertal development and/or hypertension. Although hypertension seems to develop during childhood as shown in the present case, it is seldom recognized at young ages, since blood pressure is not necessarily measured routinely in pediatric practice. In the present case, hypertension was recognized in childhood during careful follow-up after development of Kawasaki disease. Furthermore, herniation of the gonad also gave us another chance to perform detailed studies for the diagnosis of the underlying disorder.

ACTH stimulation test undergone at the age of 6.1 years was essential for the diagnosis of 17α-hydroxylase deficiency. Moreover, molecular genetic study added a more direct confirmation. Expression studies of this particular type of compound heterozygote are now under way. Although in most cases of this disorder increased production of DOC in the zona fasciculata results in suppression of both PRA and aldosterone production in zona glomerulosa [5, 6], the aldosterone level was not suppressed in the present case. Similar findings have also been reported in this disorder particularly from Japan [3], but the exact mechanisms of this aldosterone production are still unknown.

It is of note that adrenal crisis is unusual despite impaired cortisol production in 17α-hydroxylase deficiency. Only four cases of adrenal insufficiency have been reported associated with this disorder [7–10]. Indeed, the episode of adrenal insufficiency was not present in our patient even on the occasion of Kawasaki disease or the operation for inguinal hernia. In patients with 17α-hydroxylase deficiency, ACTH level increases because of impaired cortisol production in the zona fasciculata, and high plasma ACTH in turn stimulates the production of corticosterone as well as DOC in the zona fasciculata. Since corticosterone has significant glucocorticoid effects, adrenal crisis seems to be unusual. As shown in Table 2, ACTH and corticosterone levels increased just before the next dexamethasone administration during alternate-day regimen. This implies that, at the time of decreased dexamethasone, increased corticosterone is likely to work as a “back-up” glucocorticoid, so that alternate-day dexamethasone administration can be considered a safe and unique treatment for 17α-hydroxylase deficiency.

To our knowledge, growth patterns of children with 17α-hydroxylase deficiency have not been reported whether with or without treatment. Nevertheless, it is presumed that the final height of the untreated patients with the complete type of this disorder will become tall, because the epiphyseal fusion does not occur in the absence of estrogen [11]. Indeed, this assumption was proved by an analysis of the previously reported cases [5, 8, 12–17]. Their mean adult height SD scores calculated with the standard in each corresponding country was close to the mean for healthy males and much higher than that for females irrespective of their karyotype (Fig. 2). This tallness, however, is an unacceptable outcome not simply because of being too tall for girls but because of persistent hypertension and absent sexual development which have been left untreated.

On the other hand, it is also of great concern to us that glucocorticoid therapy, if it is introduced in childhood, may cause growth impairment. The present case, in fact, showed a remarkable growth deceleration during the therapy with daily

### Table 2. Changes in adrenal hormone levels on two consecutive days during alternate-day dexamethasone therapy

<table>
<thead>
<tr>
<th>Hours after dexamethasone administration (clock time)</th>
<th>day 1</th>
<th>day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.5 (1630 h)</td>
<td>24 (0800 h)</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>DOC (ng/ml)</td>
<td>0.07</td>
<td>0.04</td>
</tr>
<tr>
<td>Corticosterone (ng/ml)</td>
<td>0.95</td>
<td>1.17</td>
</tr>
<tr>
<td>Aldosterone (pg/ml)</td>
<td>107.2</td>
<td>127.3</td>
</tr>
<tr>
<td>Cortisol (µg/dl)</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>PRA (ng/ml/h)</td>
<td>6.46</td>
<td>4.52</td>
</tr>
</tbody>
</table>

0.5 mg of dexamethasone was given at 0800 h on day 1. DOC, deoxycorticosterone; PRA, plasma renin activity.
administration of 0.25 mg dexamethasone. In this context it should be noted that the growth rate was restored during the first two years of alternate-day regimen of 0.5 mg dexamethasone. Although the growth rate again became reduced thereafter, it was improved by the concomitant use of low-dose estrogen (62.5 μg of conjugated estrogens). This implies that very low levels of estrogen are required for normal growth even before the onset of puberty. With increasing dosage of estrogen, the pubertal growth spurt was achieved without rapid acceleration of bone maturation. Furthermore, the peak height velocity was close to the mean for Japanese girls. The patient's height is now approaching the target height for a boy, suggesting that the modes of therapy employed did not decrease growth potential.

We conclude that (1) alternate-day administration of dexamethasone is a safe and effective treatment for childhood 17α-hydroxylase deficiency to attain good control of blood pressure, minimal risk of adrenal insufficiency, and unimpaired prepubertal growth, and (2) concomitant use of gradually increased dosage of estrogen results in a sufficient peri-pubertal growth rate, intact pubertal growth spurt and, accordingly, final favorable statural prognosis.

References


Fig. 2. Final height SD scores of untreated adult patients in the literature who were considered to have complete 17α-hydroxylase deficiency. Height SD scores were calculated based on the female (2a) and male (2b) standards. Values are expressed as the mean ± SD. Statistical analysis was performed with Student's t-test.


