Pituitary gonadal axis and child rate in males with classical 21-hydroxylase deficiency

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ABSTRACT. Though appropriate glucocorticoid substitution therapy should abolish both cortisol deficiency and adrenal androgen excess in patients with 21-hydroxylase deficiency (21-OHD), the long-term outcome is not always satisfactory. There are several reports on low adult height in both male and female patients, and impaired fertility has been reported in females with 21-OHD. There are only few reports on gonadal function of adult male patients with 21-OHD. In this study, we calculated the child rate of all the 29 diagnosed adult Finnish males with classical 21-OHD and compared it with the mean child rate of the whole Finnish male population with equal age distribution. Sixteen males with 21-OHD and their age-matched healthy controls were further examined in a cross-sectional study. Auxology and pituitary gonadal axis were examined in both patients and controls. Testicular ultrasonography of the patients was also performed. The mean child rate of the 29 males with 21-OHD was 0.07 which was significantly lower ($p<0.001$) than that in the Finnish male population of the same age (0.34). In the cross-sectional study, males with 21-OHD had serum testosterone, inhibin B, LH and FSH concentrations comparable to those of healthy controls and reference values. Serum DHEA-S concentrations were remarkably low, even in the undersubstituted males with 21-OHD ($p<0.001$, compared with the healthy controls). In the patient group, serum inhibin B concentration did not correlate with serum FSH concentration. Adrenal rest tumors of the testicles were found in two undersubstituted males with 21-OHD. In conclusion, our study suggests normal pituitary and gonadal function but reduced child rate in adult males with 21-OHD. This might be explained by suboptimal psychosocial adaptation to the chronic disease. However, the patients in this study were young and the final child rate may become essentially higher.

(J. Endocrinol. Invest. *23:* 23-27, 2000)

INTRODUCTION

The incidence of classical 21-hydroxylase deficiency (21-OHD) in Finland as in most other Caucasian populations is about 1:15,000 live births. More females than males are diagnosed in countries which do not screen 21-OHD in the neonatal period (1, 2) and the age distribution of these patients differs from the general population as severely affected patients used to succumb before the era of glucocorticoids (1). Several studies have focused on fertility and ovarian function of females with 21-OHD (3-5), whereas only little interest has been paid to the fertility and gonadal function of males with 21-OHD (6). On the other hand, adrenal rest tumors have been found in 1:10 males with 21-OHD (7-12). These benign tumors are often related to suboptimal glucocorticoid substitution doses and they usually disappear when the hormone substitution is optimised (9, 13). Adrenal rests have been shown to lead to temporary infertility (14, 15) but it is not known if they can cause permanent testicular failure. In females with 21-OHD, prenatal exposure to adrenal androgens has been suggested to lead to masculinization of central nervous system and there are some reports on decreased interest in the opposite sex (16, 17). As adrenal androgens apparently do not have such an effect on males, 21-OHD males have not been examined with such an intensity. To date, there are only few reports on long-term psychosocial outcome in males with 21-OHD. The aim of this study was to examine the child rate of all the adult male patients with 21-OHD diagnosed in Finland. In order to evaluate the pituitary gonadal axis, 16 male patients were compared with age-matched healthy controls in a cross-sectional study.

Key-words: 21-hydroxylase deficiency, congenital adrenal hyperplasia, fertility, male.

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Accepted October 24, 1999.

PATIENTS AND METHODS

This study was carried out in Kuopio University Hospital. The study protocol was approved by the local ethical committee. Patients with 21-OHD were sought in all the five universities and sixteen central hospitals existing in Finland. Diagnosis registers and personal contacts were used to locate the patients. A total of 29 male patients with 21-OHD, aged at least 16 years and completed puberty, were found. Of these patients 16 males were able and willing to participate in the cross-sectional study. These males were compared with 16 age-matched healthy controls. Background data of the 16 males with 21-OHD are presented in Table 1. All these patients were substituted with glucocorticoids (hydrocortisone, prednisone, prednisolone or dexamethasone). Patients with a salt wasting form of 21-OHD or with milder mineralocorticoid deficiency, as evidenced by elevated plasma renin activity, were receiving mineralocorticoids (9-α-fluorocortisol). All the males had previously been genotyped and their genotypes could be linked with classical 21-OHD (2). The child rate of the patient group (no.=29) was compared with that of the whole Finnish male population with equal age distribution (18). The examination of the 16 patients and their controls involved auxology, biochemical investigations, and for the patients testicular ultrasonography. Height was measured with a Harpenden stadiometer and weight was recorded. All the blood samples were collected at 8:00 h after 8-h fasting and for the patients prior to their morning medication. Serum concentrations of androstenedione (A4), dehydroepiandrosterone sulfate (DHEA-S), testosterone (T), and 17α-hydroxyprogesterone (17-OHP) were determined by RIA (Diagnostic Products Corporation, Los Angeles, CA, USA). Serum concentrations of prolactin (PRL), follicle stimulating hormone (FSH), and luteinizing hormone (LH) were determined by chemiluminescent enzyme immunoassay (Diagnostic Products Corporation). Serum inhibin B concentrations were determined by ELISA (Serotec Ltd., Oxford, UK) and those of serum sex hormone binding globulin (SHBG) by IRMA (Orion Diagnostica, Espoo, Finland). Free testosterone (T free) concentration was calculated with the method of Anderson from serum T and SHBG concentrations (19). Student's *t* test was used to compare the mean child rate of the patients with 21-OHD with that of the normal population and to compare variables between the 16 patients and their age-matched controls. Pearson's correlation test was used to study the linear correlation between serum inhibin B and serum FSH concentrations. The significance level was set to 0.05.

Table 1 - *Patient characteristics of the 16 males with 21-OHD taking part in the cross-sectional study.*

Case	Age (yr)	Medication (mg/d)	Serum A4 (nmol/l)	Serum 17-OHP (nmol/l)	Form	Genotype[1]
1	28	D 1; F 0.4	1.1	3.2	SW	30 kb del/5' end conv
2	33	D 1; F 0.2	1.6	23.2	SW	del or conv/del or conv
3	28	HC 25; F 0.15	73.0	1130.0	SW	3' end conv/del or conv
4	28	HC 20+10+10; F 0.1	3.8	4.6	SV	I172N/del or conv
5	18	HC 10+10+20; F 0.05	2.5	4.1	SW	I172N+P453S/30 kb del
6	28	D 0.5	1.6	4.6	SV	del or conv/I172N
7	16	HC 15+10+5	3.4	86.0	SV	I172N/I172N or del or conv
8	20	HC 10+10+10; F 0.05	2.9	41.7	SV	I172N/I172N or del or conv
9	21	HC 7.5+7.5+10; F 0.1	2.8	5.4	SV	I172N/del or conv
10	21	P 5	2.6	9.1	SV	I172N/I172N
11	32	HC 10+20; F 0.1	32.9	247.0	SW	30 kb del /30 kb del
12	29	P 7.5+2.5; F 0.05	12.2	173.0	SW	2 splice/1 splice or del or conv
13	20	P 5+5; F 0.1+0.1	7.2	202.0	SV	I172N/I172N
14	28	HC 10+10+10; F 0.05	16.5	262.0	SW	30 kb del/30 kb del
15	20	HC 10+10+10	12.7	321.0	SV	30 kb del/I172N
16	36	HC 10+5+5	46.6	1210.0	SV	I172N/del or conv

D=dexamethasone; P=prednisone or prednisolone; HC=hydrocortisone; F=9-α-fluorocortisol; SW=salt wasting; SV=simple virilizing.
[1]Jääskeläinen *et al.* (2).

Table 2 - *Comparison between the 16 men with 21-OHD and the control group. Also the local reference values are given. Reference height for the healthy Finnish males is expressed as the mean±SD. Group values are expressed as means (95% confidence intervals).* P-*values are based on Student's* t *test.*

	Patients	Controls	*p*
Age (yr)	25.4 (22.3-28.6)	25.7 (22.7-28.7)	NS
Height (cm) 178.9±6.6	170.1 (165.1-175.1)	179.4 (176.9-181.9)	0.002
BMI (%) 20-25	25.8 (22.7-28.9)	23.9 (22.0-25.8)	NS
Serum A4 (nmol/l) 2-7	14.0 (3.2-24.8)	7.9 (6.9-9.0)	NS
Serum DHEA-S (umol/l) 2-12	1.1 (0.8-1.4)	7.8 (6.7-8.8)	<0.001
Serum LH (IU/l) 0.8-7.6	3.9 (2.8-5.0)	2.8 (2.0-3.5)	NS
Serum FSH (IU/l) 0.7-11.0	3.4 (2.4-4.3)	2.2 (1.4-3.0)	NS
SerumT (nmol/) 14-33	18.9 (15.2-22.6)	18.0 (15.5-20.6)	NS
Serum SHBG (nmol/l) 10-50	28.1 (21.9-34.2)	23.4 (19.4-27.5)	NS
Serum T free (pmol/l) 180-600	313.4 (259.3-367.6)	316.7 (282.5-350.9)	NS
Serum PRL (mU/l) 55-520	245.6 (186.6-304.5)	275.9 (230.0-321.9)	NS
Serum inhibin B (ng/l)	139.9 (117.8-161.9)	153.2 (132.1-174.2)	NS

RESULTS

The child rate of the 29 CAH males was 0.07, which was significantly (p<0.001) lower than the mean child rate 0.34 in the Finnish male population with equal age distribution (18). A comparison between the 16 males with 21-OHD and their age-matched controls taking part in the cross-sectional study is presented in Table 2. The males with 21-OHD were shorter and they had serum DHEA-S concentrations lower than the controls. On the other hand, no significant difference could be detected in mean serum concentrations of FSH, LH, prolactin, testosterone, SHBG, androstenedione or inhibin B. As presented in Figure 1, serum inhibin B concentration correlated significantly with that of FSH in the control group (r=-0.537; p=0.03) but not in the patient group (r=-0.014; p=0.96). Twelve (75%) of the 16 male patients studied had normal scrotal ultrasonography finding. Two patients (12.5%) had bilateral adrenal rest tumors. They were both clearly undersubstituted with glucocorticoid, evidenced by elevated serum A4 (32.9 and 16.5 nmol/l) and 17-OHP concentrations (247.0 and 262.0 nmol/l). One patient had bilateral varicocele and one had mild hydrocele.

DISCUSSION

It has previously been reported that male patients with 21-OHD have subnormal adult height (6). Adrenal rest tumors have also been well documented (7-12). Otherwise, it has been thought that 21-OHD males have a relatively favorable prognosis. When appropriately substituted, they should have sperm counts and bone mineral densities (BMD) within normal range (6, 20). It has been speculated whether males with a mild form of 21-OHD would do well even without glucocorticoid substitution as far as fertility is concerned (6). Against this background, it is understandable why most previous studies on long-term outcome of CAH patients have been carried out for females only. As androgen excess with all its consequences is an unphysiological state for females, their psychosexual orientation has been of great interest and psychological support is routinely offered for girls with 21-OHD. Unlike with women, psychological evaluation of male patients has largely been neglected. We detected low child rate in the presence of normal pituitary gonadal axis in male patients with 21-OHD suggesting poor psychosocial adaptation to the chronic disease. The patients in this study

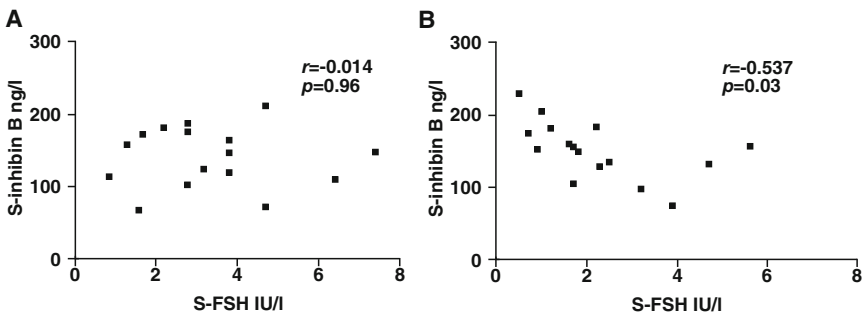

Fig. 1A and 1B - *Serum inhibin B concentrations (ng/l) in relation to serum FSH concentrations (IU/l) in the sixteen 21-OHD males (A) and sixteen age-matched control males (B).*

were relatively young and the final child rate may become significantly higher but we still find it useful to offer psychological support and even more detailed councelling also for males with 21-OHD. Our hypothesis was that supranormal adrenal androgen secretion might have some effect on the hypothalamo-pituitary-gonadal axis. In this study, sperm counts were not evaluated. Thus, we cannot state that our males with 21-OHD have normal sperm counts and fertility. However, in accordance with the study of Urban *et al.* (6), it seems that in the majority of patients adequately treated, 21-OHD does not lead to impaired function of either Sertoli or Leydig cells. The negative correlation between serum inhibin B and FSH concentrations found in healthy male populations (21, our control group) could not be found in the patient group. This suggests that in males with 21-OHD the normal regulation of FSH secretion is somehow disturbed. The abnormal steroid profile in 21-OHD males may disturb the normal control of FSH secretion but further studies are required to resolve this question. Extremely low DHEA-S concentrations were found in all males, even in undersubstituted patients. The same phenomenon has previously been observed in children and adult females (4, 22, 23). It has not been fully clarified why the adrenal reticular zone does not produce DHEA-S while the output of androstenedione is supranormal. One explanation could be increased 3-β-hydroxysteroid dehydrogenase activity in the adrenals of 21-OHD patients. We recommend regular follow-up once a year also for adult 21-OHD males. As adrenal rest tumors are not necessarily palpable, testicular ultrasonography should be included in the routine examination. Detailed counceling about the nature and prognosis of 21-OHD is of great importance also for adult males with 21-OHD.

ACKNOWLEDGMENTS

This study was supported by the Foundation for Pediatric Research, Helsinki, Finland.

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