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Hypogonadotropic Hypogonadal Men Respond Less Well to Androgen Substitution Treatment than Hypergonadotropic Hypogonadal Men

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This research asked whether androgen substitution therapy is as efficacious in hypogonadotropic hypogonadal men as in hypergonadotropic hypogonadal men. Erotosexual functions of two groups of six men of each diagnostic category were compared after 5–6 years of continuous androgen treatment. Treatment regimen was the same in both groups: Parenteral testosterone esters 250 mg/2 weeks. No difference was found in erectile and ejaculatory potency, but the number of sexual acts and scores of subjective quality of sexual acts, sexual excitement, and frequency of sexual thoughts and of non-sexual parameters as vigor, fatigue, anxiety were more negative in the hypogonadotropic men. The most obvious difference between the two groups is the value of LH/FSH and presumably of LHRH. Hypogonadotropic hypogonadal men may be better treated with gonadotropins (or with pulsatile LHRH, when the hypophysis is intact) than with androgens.

KEY WORDS: gonadotropins; androgens; sex functions.

INTRODUCTION

In recent years well-designed double-blind studies have established that some parts of the spectrum of adult male sexuality are androgen-dependent. (For reviews see Bancroft, 1984, and Davidson *et al.*, 1982.) Androgen-

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deficient men clearly benefit from substitution therapy with adequate dosages of androgen hormones.

Etiologically, two types of androgen deficiency can be distinguished:

1. Primary hypogonadism: In this category the testis fails to produce sufficient amounts of androgens; hypothalamic and hypophyseal hormones responsible for testis stimulation circulate in elevated quantities in the peripheral blood, since they are unopposed by the negative feedback action of testicular hormones.

2. Secondary hypogonadism is due to an insufficient stimulation of an intact testis by hypothalamic/hypophyseal hormones. This type may be congenital (absence of LHRH-producing neurons and hyposmia/anosmia as in Kallmann's syndrome) or acquired later in life (a tumor or granulomatous process destroys LHRH-producing neurons and/or LH/FSH-producing hypophyseal cells).

The first type has also been termed hypergonadotropic and the second type hypogonadotropic hypogonadism. It is evident that both categories benefit from androgen treatment with regard to physical virilization and erotosexual development (Davidson *et al.*, 1982; Skakkebaek *et al.*, 1981).

This study attempted to assess whether androgen replacement therapy is as efficacious in hypogonadotropic men as in hypergonadotropic men with regard to the development of erotosexual functions in the adolescent male. We asked whether there is evidence that, apart from androgens, other hormones (LHRH, LH/FSH) play a role in the process of erotosexual development. Results might imply different therapeutical measures for the two categories of patients.

SUBJECTS AND METHODS

We compared two groups of six men: the first consisted of six hypergonadotropic hypogonadal men and the second of six hypogonadotropic men. All were first seen at our clinic in 1977–1978. In all men basal levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T), and prolactin were measured.

Serum LH and FSH concentrations were determined by double-antibody solid-phase RIA (IRE, Fleuris, Belgium), using standards calibrated with MRC 68/40 and 68/39 preparations, respectively. The intraassay coefficient of variation (CV) was 7% for LH and 5% for FSH and the interassay cvs were 11 and 12%, respectively. Serum T concentrations were measured by RIA using a 7-alpha-conjugated estrogen-thioether testosterone antiserum. The intra- and interassay cvs were 9.1 and 12.5%, respectively. Serum prolactin concentrations were determined by double-antibody RIA (IRE, Fleuris,

Belgium), using standards calibrated with the MRC 71/122. The intra- and interassay cvs were 5.8 and 7.4%, respectively. Details are provided in Table I.

At the time of their first visit to the clinic for assessment of insufficient development of male sex characteristics, the men were between 14 and 18 years. Since procreation was not viewed at this stage by these patients, masculinization was induced with testosterone esters (Sustanon-250), one injection per 2 weeks. None had previously been treated with testosterone or gonadotropins.

Partial or total loss of testis function in the hypergonadotropic hypogonadal group had occurred before age 12. There were no obvious differences in pubertal development between the two groups. None of the subjects had progressed beyond stage P2 of the rating of Tanner and Whitehouse (1976).

Erotosexual functions were assessed 5 to 7 years after the start of this treatment and a comparison was made between the two groups. The methods of assessment of sexual behavior were those presented in the report of Skakkebaek *et al.* (1981). With regard to erotosexual functions the following information was obtained: (i) sexual acts (coitus or masturbation) on a day-to-day basis; (ii) ejaculation: Does a sexual act result in ejaculation?; (iii) subjective quality of sexual acts, rated on 1–4 scale (1 = unpleasant, 4 = very satisfactory; (iv) erection 0–4 scale (0 = never an erection while awake, 4 = erections sufficient for intercourse in over 75% of occasions).

Weekly self-ratings were made of: (i) frequency of sexual thoughts (0–4 scale); (ii) the extent to which these thoughts were associated with excitement (0–2 scale); (iii) mood, using the Lorrand McNair mood checklist (McNair *et al.*, 1964) providing scales for anxiety, tension, depression, anger, vigor, and fatigue.

To compare the mean values of the two populations a one-factor analysis of variance was applied followed by the two-sample *t* test (Petrie, 1978). A p value of 0.05 was chosen as a limit of statistical significance. All subjects had T values below reference values of eugonadal men.

RESULTS

Results are presented in Tables I and II. Table II demonstrates that the scores in hypogonadotropic hypogonadal men were significantly lower with regard to the number of sexual acts per week, subjective quality of sexual acts, frequency of sexual thoughts, and sexual excitement. There were no more erectile or ejaculatory problems in the hypogonadotropic men, but they scored more negatively on the nonsexual androgen-related items of anxiety/tension, anger, vigor, and fatigue.

Table I. Comparison of Data on Two Groups of Hypogonadal Men

Diagnosis	Age of start of treatment	T nmol/L	LH U/L	FSH U/L	Prolactin U/L	Other hypophyseal deficiencies
Normal range		10–24	4–8	4–8	0.04–0.30	
Data on six hypogonadotropic hypogonadal men						
Kallman syndrome	16	3.0	2.0	1.4	0.09	
Kallman syndrome	17	4.5	1.5	3.0	0.14	
Kallman syndrome	17	3.4	2.4	1.5	0.16	
Sarcoidosis hypothalamus	15	4.9	3.9	3.2	0.14	ADH (carbamazepine)
Craniopharyngeoma	15	2.5	1.9	2.5	0.11	TSH (levothyroxine)
Craniopharyngeoma	16	3.9	1.5	2.6	0.17	
Data on the six hypergonadotropic hypogonadal men						
Bilateral torsio testis	14	2.0	24	41	0.12	
Cryptorchidism left + torsio testis	15	1.5	27	35	0.17	
Retentio testis	16	4.0	20	40	0.18	
Orchidectomy (testis malignancy)	15	3.0	24	38	0.16	
Mumps orchitis	15	4.6	24	36	0.12	
Hematoma of scrotum + testis atrophy	14	3.9	23	29	0.11	

Table II. Erotosexual Functions Compared in Two Groups of Hypogonadal Men Treated With Androgens for 5–6 Years[a]

	Hypergonadotropic hypogonadal men	$p <$	Hypogonadotropic hypogonadal men
No. of sexual acts per week	4.2 ± 1.3	0.05	2.5 ± 1.1
No. of ejaculations per week	3.0 ± 1.1	0.05	1.6 ± 0.9
Subjective quality of sexual acts	3.0 ± 1.0	0.05	1.9 ± 1.1
Frequency of sexual thoughts per week	2.4 ± 0.8	0.05	1.5 ± 0.6
Frequency of sexual excitement	1.3 ± 0.4	0.05	0.8 ± 0.3
Erectile problems (0–4)	2.7 ± 1.0	ns	2.8 ± 1.1
Ejaculatory problems (0–4)	1.0 ± 0.3	ns	1.1 ± 0.4
Anxiety and tension (9–36)	14.5 ± 3.0	0.05	19 ± 4.0
Depression (12–48)	18 ± 4.0	ns	17 ± 5.1
Anger (8–32)	14 ± 3.0	0.05	10 ± 2.5
Vigor (6–24)	16 ± 4.1	0.05	12.2 ± 3.6
Fatigue (6–24)	14 ± 3.0	0.05	16 ± 4.2

[a]Data are presented as means ± SD.

DISCUSSION

This study attempted to assess whether androgen substitution treatment is equally efficacious in hypogonadotropic hypogonadal men as in hypergonadotropic hypogonadal man. Both groups had been examined in our clinic when they were in a comparable state: androgen-deficient and no previous sexual experience. A potential bias towards better sexual functioning of the hypergonadotropic hypogonadal group on testosterone treatment may lie in the fact that this group had probably not been deprived of the effects of testosterone in early childhood. Postnatal testosterone levels rise to early pubertal values.

Considerable differences were found between the two groups after 5 to 6 years of androgen therapy with the same dosage regimen. Erection and ejaculation proved equally satisfactory in both groups, but all other parameters were more negative in the hypogonadotropic men. It is tempting to speculate that more than the other parameters, erection and ejaculation depend on the peripheral action of androgens, whereas the biological substrate of the other parameters (libido, etc.) is more likely to be located in the central nervous system, though a strong interdependency is likely to exist (Davidson *et al.*, 1982). The most obvious difference between the two groups is the level of the gonadotropic hormones LH/FSH and putatively of the hypothalamic hormone LHRH. Since ACTH secretion was not impaired in any of the hypogonadotropic men, it is unlikely that adrenal androgens account for the difference between the two groups. Prolactin levels were not higher in the hypogonadotropic men than in the hypergonadotrop-

ic men. Elevated prolactin levels interfere with sexual functions in the male. Several observations in animals have indicated that LHRH might contribute to mating behavior (Moss and McCann, 1973; Dorsa *et al.*, 1981). There is also preliminary evidence that libido is positively influenced by exogenous LHRH (Moss *et al.*, 1979; Davies *et al.*, 1976). In these studies no effect was noted on erectile potency. There are several reports that virilization and erotosexual behavior develop sluggishly in men with panhypopituitarism (Money and Clopper, 1975; Money *et al.*, 1980) upon treatment with androgens. From data on four men, consecutively treated with androgens and gonadotropins, Clopper *et al.* (1983) concluded that induction of virilization and possibly also of erotosexual function proceeds more favorably with gonadotropin therapy than with androgens alone in hypogonadotropic men.

Further studies are needed to verify whether the interests of hypogonadotropic hypogonadal men are better served with gonadotropin therapy (or its modern version pulsatile LHRH therapy, when the hypophysis is intact) than with androgen therapy alone.

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