Journal of Andrology, Vol. 11, No. 6, November/December 1990

Male Hypogonadism Due to Nontumorous Hyperestrogenism

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Male hypogonadism due to the nontumorous production of estrogen was studied in a patient with gynecomastia and bilateral small testicles. Both the gynecomastia and the decrease in testicular size developed in the 5-year period before presentation. Peripheral serum concentrations of testosterone were in the low to low-normal range, while those of 17β-estradiol (E2) were significantly elevated, as were the urinary concentrations of total estrogen. Steroid hormone concentrations were measured in the left and right spermatic veins and the left and right adrenal veins in the basal state, and after stimulation with GnRH and ACTH. Spermatic vein concentrations of E2 were 3 to 20 times higher than concentrations previously reported in normal males. Spermatic vein concentrations of testosterone were normal. The spermatic vein concentrations of androstenedione were approximately three times higher than the mean concentration of androstenedione previously reported in the spermatic vein of normal males. The concentrations of E2 and androstenedione in the adrenal veins were also significantly elevated when compared to the concentrations previously reported in normal subjects. The authors postulate that the hyperestrogenism in this patient was due to increased aromatization of the precursor substrates, testosterone in the testes, and androstenedione in the adrenals to E2 and E1 in the testes and adrenals, respectively. Alternatively, an increased abundance or activity of the 17β-hydroxysteroid dehydrogenase isoenzyme which converts estrone (E1) to E2 or a relative deficiency of the 17β-hydroxysteroid dehydrogenase isoenzyme, which converts androstenedione to testosterone, could theoretically account for the reported abnormalities.

Key words: LH, FSH, estradiol, spermatic vein, adrenal vein, feminization.

J Androl 1990; 11:485–490.

Male hypogonadism due to an excess of estrogen has been described, but not commonly recognized as a cause of male hypogonadism (DeGroot, 1979). Cases of male hypogonadism associated with hyperestrogenism reported previously have described patients with benign (nontumorous) conditions (Valenta and Elias, 1986a; Valenta, 1977), and a patient with an adrenal estrogen-producing tumor (Veldhuis et al, 1985). Male hypogonadism resulting from excess estrogen or combined estrogen–progestogen administration (Valenta and Elias, 1989) has also been observed in a number of cases. The general features of estrogen-induced male hypogonadism are hypogonadotropism, erectile impotence, a variable degree of feminization, and a decrease in androgenization, all of which are reversible upon normalization of elevated plasma estrogen concentrations.

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Received for publication February 8,1990; accepted for publication June 4, 1990.

This report aims to better describe estrogen-induced male hypogonadism. It is the first documentation of a case in which hormone levels in a patient with estrogen-induced hypogonadism have been measured in the spermatic veins, as well as in the peripheral and adrenal veins in both the basal and stimulated states.

Materials and Methods

Case Report

The patient was a 35-year-old man who was referred for the evaluation of an estrogen-producing tumor. His chief complaints at the time of examination were nontender bilateral breast enlargement of approximately 5 years' duration, increasingly prominent breast enlargement and a decrease in libido for the past 2 years. He was employed as an engineer and denied the use of any prescription or nonprescription medications or drugs. The patient denied galactorrhea, a decrease in the frequency of shaving, erectile impotence, or any subjective decrease in testicular size. He could not recall having suffered any trauma to his testicles and did not remember experiencing testicular pain and swelling that would have suggested viral orchitis. The patient had three younger brothers and two younger sisters. None of his siblings was married, and he was unaware of gynecomastia developing in any of his male siblings or other male family members.

The patient was a slightly built individual (weight, 63 kg; height, 162 cm) with normal body proportions (symphysis to heels, 88 cm; arm span, 165 cm). The testicles were small and soft (left, 3 cm; right, 3.5 cm) with no palpable masses. There was bilateral moderate gynecomastia with no galactorrhea. The penis was of normal size and pigmentation. The body hair was appropriate for the patient's ethnic background and he did not exhibit fat distribution of a female body type. There was no clinical evidence of renal, hepatic, or neurologic diseases, or laboratory evidence of renal or hepatic diseases.

Stimulation Tests

In order to assess the integrity of the hypothalamic–pituitary axis, a clomiphene stimulation test was performed. On the fifth day of clomiphene citrate administration (100 mg/d, orally), the peripheral serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations were measured.

Before stimulation (IV bolus) with adrenocorticotropic hormone (ACTH) and gonadotropin-releasing hormone (GnRH), the serum concentrations of adrenal and testicular hormones were measured in the peripheral blood, in the right and left adrenal veins, and in the right and left spermatic veins. The concentrations of steroids in the spermatic veins were measured again at 20 and 45 minutes, and in the adrenal veins 20 minutes after stimulation. The dose of ACTH employed was 0.25 mg of β1-24 ACTH; the dose of GnRH was 100 μg. The ACTH and GnRH stimulation tests were performed in one session. ACTH stimulation was performed first. After the sampling catheters were positioned in the adrenal veins, blood for baseline hormone concentrations was collected. After ACTH stimulation, blood was collected for the measurement of stimulated hormone concentrations. The sampling catheters were then positioned in the spermatic veins and approximately 45 to 60 minutes later (the time required to reposition the catheters) baseline and GnRH stimulated blood samples were collected for hormone measurements.

Laboratory Studies—Radiologic studies performed elsewhere included an intravenous pyelogram, a computed tomographic (CT) scan of the abdomen, and a chest x-ray. The results of all studies were normal.

Specific radioimmunoassays of testosterone estrogens and gonadotropins were performed by a commercial laboratory (Endocrine Sciences, Tarzana, CA). Steroid hormones in the spermatic vein and adrenal vein sera were separated by column or paper chromatography prior to measurement by specific radioimmunoassays. The karyotype was that of a normal male (46XY).

Results

Clomiphene Stimulation

After the administration of clomiphene citrate, the peripheral serum LH and FSH concentrations increased to 22.6 mIU/ml and 52.6 mIU/ml, respectively, suggesting normal integrity of the hypothalamic–pituitary axis.

Peripheral Baseline Concentrations of Testosterone, Estrogen, and Gonadotropins

Normal values are indicated in parentheses. Total urinary estrogen content was 47.6 and 45.8 μg/24 hours (5–25) on two separate occasions. Serum estriol (E3), 17β-estradiol (E2), and estrone (E1) concentrations were 100 pg/ml (0–100), 270 pg/ml (8–38), and 73.6 pg/ml (30–170), respectively. Total serum estrogens were 444 pg/ml (40–115). Human chorionic gonadotropin (β-hCG) concentration was undetectable. Serum LH and FSH concentrations were 9.3 mIU/ml (3–10) and 17 mIU/ml (1–8), respectively. Serum testosterone and prolactin concentrations were measured several times and ranged from 2.7 to 4.5 ng/dl (3–12), and 9 to 16 ng/ml (< 20 ng/ml).

Peripheral serum concentrations of dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEA-S) and androstenedione(A) were

10.7 ng/ml (1.6–8.0 ng/ml), 2.86 μg/ml (1.0–4.5 μg/ml), and 4.14 ng/ml (0.75–2.05 ng/ml), respectively. Peripheral serum progesterone and aldosterone concentrations were 1.3 ng/ml (0.13–0.97 ng/ml) and 0.25 ng/ml (0.03–0.16), respectively.

Gonadotropin Response to GnRH

Twenty minutes after GnRH stimulation, peripheral serum LH and FSH concentrations rose from baseline concentrations of 9.3 mIU/ml and 17 mIU/ml, respectively, to 35 mIU/ml and 41 mIU/ml, respectively. LH and FSH concentrations, 45 minutes after GnRH stimulation, were 24 mIU/ml and 55 mIU/ml, respectively.

Steroid Hormone Concentrations in Adrenal and Spermatic Veins

Serum E2 concentrations were 3 to 20 times higher than E2 concentrations previously reported in young, otherwise healthy males with hypertension (Longcope et al, 1972) and in males with hypogonadism (Kelch et al, 1972). Serum concentrations of testosterone in the spermatic veins were lower than the values previously reported in healthy individuals (Hammond et al, 1977).

Data on steroid hormone levels in the spermatic veins after GnRH stimulation have not been previously reported. In our patient, GnRH administration caused a marked increase in all measured steroid hormones except DHEA-S. This elevation of steroid hormone concentrations occurred as early as 20 minutes after GnRH administration. In most instances, the levels doubled when compared to baseline values (Table 1). The different response kinetics, as well as the different individual hormone responses, in the two anatomic sides are of unknown significance.

ACTH stimulation of the adrenal steroids was also performed to examine the role of the adrenal glands as a possible source of the elevated peripheral estrogens. The results are summarized in Table 2. In comparison to our previously reported findings in women (Valenta and Elias, 1986b), the results show elevation of the baseline plasma E1, E2, and A concentrations. ACTH-stimulated peripheral concentrations of steroid hormones are shown in Table 3.

Discussion

Measured peripheral blood levels of specific androgens and estrogens each represent the sum of the hormones directly secreted from the adrenal glands and gonads, in addition to those derived from the peripheral conversion of appropriate hormone precursors. Such hormone conversions occur with E1 and E2, and androstenedione and testosterone, respectively (Gower and Fotherby, 1975). Although the secretion of estrogens from testes in normal males is well studied and established (Givner et al, 1960; Morse et al, 1962; Goldzeiher and Roberts, 1952), there is no data on the secretion of estrogens from the testes of patients who have nontumorous hyperestrogenism.

This investigation shows that the testicular production of estrogens (particularly E2), inferred from measuring spermatic vein concentrations, in a patient with nontumorous hyperestrogenism

Table 1. *Plasma concentrations of testosterone (T), estrone (E_1), estradiol (E_2), progesterone (P), androstenedione (A), dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEA-S) in the spermatic veins before and after gonadotropin releasing hormone (GnRH) stimulation*

	Right testis			Left testis		
Hormone	Baseline	20 min GnRH	45 min GnRH	Baseline	20 min GnRH	45 min GnRH
T (ng/ml)	381	503	945	334	1144	950
E_1 (pg/ml)	391	562	532	331	719	783
E_2 (pg/ml)	2665	3053	5172	3467	7097	5053
P (ng/ml)	9.4	16.1	46.2	8.3	42.4	46.0
A (ng/ml)	33.0	43.7	82.0	38.7	80.6	61.5
DHEA (ng/ml)	30.4	45.4	75.9	33.4	97.8	68.1
DHEA-S (μg/ml)	3.0	2.9	2.3	2.6	2.8	3.1

Normal values based on previously published values (range) = T (285 to 619 ng/ml); E_1 (30 to 235 pg/ml); E_2 (97 to 892 pg/ml); A (0.97 to 30.18 ng/ml, mean 11.97 ng/ml); P (1.51 to 33.2 ng/ml).

Table 2. *Plasma concentrations of testosterone (T), estrone (E_1), estradiol (E_2), progesterone (P), androstenedione (A), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and aldosterone (Aldo) in the adrenal veins before and 20 minutes after adrenocorticotropic hormone (ACTH) stimulation*

	Left adrenal		Right adrenal	
Hormone	Baseline	ACTH	Baseline	ACTH
T (ng/ml)	17	18	17	22
E_1 (pg/ml)	410	1513	676	1811
E_2 (pg/ml)	70	121	74	137
P (ng/ml)	6.2	128	14.1	105
A (ng/ml)	9.4	231	13.9	287
DHEA (ng/ml)	20.4	1091	53	1089
DHEA-S (μg/ml)	4.2	5.1	5.3	6.0
Aldo (ng/ml)	24.3	160	53	105

Normal values based on previously published data in *females* (mean ± SD) = T 0.36 ± 0.15 ng/ml; E_1 195 ± 105 pg/ml; E_2 15 ± 3 pg/ml; P 2.87 ± 0.72 ng/ml; A 4.79 ± 1.52 ng/ml; DHEA 23.18 ± 17.36 ng/ml; DHEA-S 2.00 ± 0.33 μg/ml; Aldo 24.0 ± 6.9 ng/ml.

was greater than that of normal males (Longcope et al, 1972; Kelch et al, 1972). The spermatic vein concentrations in our patient were 3 to 20 times greater than the highest levels of E2 concentrations reported in the spermatic veins of normal males (Longcope et al, 1972). On the other hand, spermatic vein concentrations of testosterone in our patient were lower than those previously reported for normal men (Kelch et al, 1972).

The increased spermatic vein content of E2 in our patient suggests endogenous testicular production of estrogen. Usually, the biosynthesis of E2 proceeds along two pathways. In one, E2 is synthesized from testosterone; in the other, E2 is produced from 4-androstenedione via E1 as an intermediate (Gower and Fotherby, 1975). The testes of this patient are preferentially secreting testosterone and E2 (Table 1), while his adrenals are secreting A and E1 (Table 2). These observations strongly support increased aromatization of the precursor substrates, testosterone in the testes, and possibly, androstenedione in the adrenals, as the cause of the hyperestrogenism in this patient. Alternatively, a preferential increase in the production of E2 from 4-androstenedione, the immediate precursor of which is 17α-hydroxyprogesterone (Gower and Fotherby, 1972), may account for the biochemical findings in our patient. Favoring this hypothesis is the spermatic vein concentration of androstenedione in our patient, which was much higher than the mean androstenedione concentration noted in previous spermatic vein catheterization studies: 30–40 ng/ml vs 11.87 ng/ml (Hammond et al, 1977).

Table 3. *Plasma concentrations of testosterone (T), estrone (E_1), estradiol (E_2), progesterone (P), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and aldosterone (Aldo) in the periphery and 20 min after adrenocorticotropic hormone (ACTH) stimulation*

Steroid in peripheral vein	Baseline	ACTH
T (ng/ml)	3.0	2.7
E_1 (pg/ml)	116	301
E_2 (pg/ml)	45	52
P (ng/ml)	1.3	4.8
DHEA (ng/ml)	10.7	26.4
DHEA-S (μg/ml)	2.9	3.1
Aldo (ng/ml)	0.25	0.37

Normal unstimulated values (range) = T (3.50 to 10.30 ng/ml); E_1 (0 to 100 pg/ml); E_2 (8 to 38 pg/ml); P (0.13 to 0.97 ng/ml); DHEA (1.6 to 8.0 ng/ml); DHEA-S (1.0 to 4.5 μg/ml); Aldo (0.03 to 0.16 ng/ml).

In addition to increased aromatization of testosterone and androstenedione in the testes and adrenals, another explanation for the abnormal steroid profile seen in this patient must be considered. The conversion of androstenedione into testosterone and E1 into E2 are dependent upon the action of the enzyme 17β-hydroxysteroid dehydrogenase. It is possible that steroidogenesis in our patient proceeded from 4-androstenedione to 19-hydroxy-4-androstenedione, then to E1, and finally to E2. A number of patients with 17β-hydroxysteroid dehydrogenase deficiency have been reported, but such patients possess a female phenotype and typically demonstrate an *elevation* of plasma E1 concentration (Peterson and Imperato-McGinley, 1984; Saez et al, 1971; Saez et al, 1972; Goebelsmann et al, 1973). Such patients also typically have normal 17β-hydroxysteroid dehydrogenase activity in extragonadal tissue, such as fibroblasts. However, the enzyme 17β-hydroxysteroid dehydrogenase exists in isoenzymatic forms (Sawada et al, 1979; Kobayashi and Kochakian, 1978); the preferential synthesis of E_2 in our patient also may be explained on the basis of the relatively greater activity of the 17β-hydroxysteroid dehydrogenase isoenzyme, which leads to E2 formation from E1. Although such a condition has not been previously described, *theoretically*, this isoenzyme may be more abundant or active

in our patient. Conversely, the 17β-hydroxysteroid dehydrogenase isoenzyme, which converts 4-androstenedione to testosterone, may be relatively deficient or defective in this individual. Less likely, *concomitant* abnormalities of *both* isoenzymes also may lead to relatively greater E2 formation.

In the normal male, the negative feedback effect on LH and FSH is exerted primarily by testosterone (Swerdloff et al, 1971; Stern and Eisenfeld, 1971; Sar and Stumpf, 1972). Whether this suppression is due to a direct influence of testosterone or to the influence of testosterone-derived intermediary metabolites remains uncertain (Ginsburg and Shori, 1978; Sheridan et al, 1982). Metabolites of testosterone, such as dihydrotestosterone (DHT) and estrogens (Sheridan et al, 1982; Leiberburg et al, 1977), are examples of steroids possibly responsible for the negative feedback effect. In our patient, the brisk gonadotroph response to GnRH and clomiphene suggests that the suppressive effect is most likely related to the combined negative feedback effects of testosterone and the increased quantities of elaborated estrogens.

It is noteworthy that our patient did not demonstrate any developmental sexual abnormalities or signs of prepubertal androgen deficiency; his symptoms and gynecomastia developed over the 5 years prior to presentation. This history is consistent with an acquired or late-onset form of enzymatic deficiency, which is analogous to that thought to be present in apparently acquired forms of congenital adrenal hyperplasia (eg, 21-hydroxylase deficiency). Acquired congenital adrenal hyperplasia is well recognized in female patients who may present postpubertal hirsutism and menstrual disturbances. Since we first studied this patient, we have evaluated several others (without performing catheterization studies) with similar clinical manifestations—gynecomastia, decreased libido, and elevated serum estradiol relative to testosterone. Thus, the disorder may be more common than presently appreciated.

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Recipients of Student Awards—1990

Awards were made to the following individuals for the best platform and/or poster presentations at the 1990 Annual Meeting of the American Society of Andrology.

New Investigator Award (sponsored by the West Michigan Reproductive Institute)

Donna O. Bunch
Duke University, Durham, North Carolina
"P95, a ZP3 Receptor with Tyrosine Kinase Activity, Fractionates with Mouse Sperm Membranes that Inhibit Sperm–Zona Binding"

Student Merit Awards

Joan S. Curl
Northwestern University, Evanston, Illinois
"Disruption of LDH-C_4 Synthesis by Antisense mRNA"

Josephine Grima
The Population Council, New York City, New York
"Diverse Secretory Patterns of Rat Clusterin in Epididymis and Prostate/Seminal Vesicles During Programmed Cell Death"

Dannette R. Mattmueller
University of Virginia, Charlottesville, Virginia
"Epididymal Sulfated Glycoprotein-2 (SGP2) is Similar but not Identical to Testicular SGP2"

Stuart E. Ravnik
University of Washington, Seattle, Washington
"Serum Inhibits Follicular Fluid-Induced Sperm Capacitation"

Karush Salehi-Ashtiani
Northwestern University, Evanston, Illinois
"Expression of Ldh-c in Mouse and Rat Testes"
(photograph not available)