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The Gonadotropin Response to Synthetic Gonadotropin Releasing Factor in Patients with Testicular Cancer

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Summary. The response of LH and FSH to synthetic gonadotropin releasing factor (GRF) was investigated in 19 patients with malignant germ cell cancers of the testicle prior to radical orchiectomy. The study showed: 1. Patients with circulating beta-HCG presented with increased plasma levels of oestradiol. Base line FSH and response to GRF were significantly decreased. 2. In patients without detectable beta-HCG plasma concentrations of oestradiol and testosterone were within the normal ranges as compared to healthy age matched controls. Base line levels of FSH and LH were increased and an exaggerated response to GRF was observed. From the results of this study it can be concluded that hypergonadotropic dysfunction of pituitary-gonadal axis exists in patients with testicular cancer of germ cell origin. Beta-HCG production by tumour tissue results in hyperoestrogenism and interferes with the pituitary-gonadal axis in terms of inhibition of pituitary gonadotropin release.

Key words: Testicular cancer, Pituitary gonadotropin release, Synthetic gonatotropin releasing factor.

Introduction

Several investigations furnish evidence that alterations of endocrine profiles are associated with testicular cancer [5, 9, 13, 21, 27, 28]. Beta-HCG can be produced by the trophoblastic cells in tumours of germ cell origin [3]. It can be responsible for hyperoestrogenism, development of gynaecomastia and spermatogenetic dysfunction. Endocrine alterations in testicular cancer patients have mainly been investigated by monitoring sexual steroids and base line levels of gonadotropins. This study was designed to further elucidate dysfunctions of the pituitary-gonadal axis by assessing the response of pituitary gonadotropin secretion to synthetic gonadotropin releasing factor (GRF).

Material and Methods

The investigation was carried out on 19 patients with testicular cancer of germ cell origin (age: 18–45 yeasrs). Tumour histology was assessed according to the classification of PUGH. The TNM-System was used for staging (UICC). In pure seminomas the N-category was evaluated by lymphography and in non-seminomatous tumours by retroperitoneal radical lymphadenectomy.

On clinical examination the volume of the contralateral testicle was roughly evaluated by palpation. Before radical orchiectomy a semen sample was collected by masturbation and analysed according to the recommendations of Eliasson. The period of sexual abstinence ranged between 2 and 11 days.

GRF loading was performed in all cases between 8 and 10 a.m. in order to avoid misinterpretation of results by daily variations of pituitary response to GRF [22]. Within a 10 min interval two blood samples were collected from an antecubital vein via an indwelling catheter and 100 micrograms of synthetic gonadotropin releasing factor (GRF) were administered by a single rapid injection. Another six blood samples were taken at 10 min intervals after GRF load. In the blood samples collected prior to GRF injection the concentrations of Beta-HCG, testosterone, oestradiol and prolactin were determined together with LH and FSH. After GRF loading LH and FSH were measured only. All serum samples were kept frozen at −25 °C until the radioimmunoassays were performed using the following methods: LH, FSH testosterone [26], oestradiol [24] and prolactin [25]. Beta-HCG was analysed with a commercial Kit from Serono.

Statistical analyses were performed by the Wilcoxon Test. After GRF load the differences between the areas under the curves of LH and FSH were compared. Eighteen age-matched fertile males served as controls.

Results

1. The histological classification of the tumours showed pure seminomas in three cases and non-seminomatous or mixed tumours in 16 (Table 1). Circulating beta-HCG was found to be present in 12 patients including one pure

Table 1. Patients (n = 19)

PAT.	Age	Histology	Stage	Contralateral testis	Semen
Beta-HCG negative (not detectable)					
M. P.	33		$T_3N_0M_0$	normal	normozoospermia
E. R.	33		$T_3N_0M_0$	normal	normozoospermia
A. R.	23	MTU	$T_3N_0M_0$	normal	Oligozoospermia
A. J.	18	MTU	$T_4N_1M_0$	normal	Oligozoospermia
R. A.	22	MTI	$T_2N_0M_0$	Atrophy	Severe Oligozoospermia
B. F.	48	MTU	$T_4N_2M_0$	Atrophy	Azoospermia
D. A.	28	MTU + S	$T_3N_1M_0$	normal	Oligozoospermia
Beta-HCG positive (135–3220 mIU/ml)					
M. J.	44	S	$T_3N_2M_0$	Atrophy	Severe Oligospermia
Z. F.	21	MTU	$T_2N_0M_0$	Atrophy	Severe Oligospermia
V. O.	45	MTU + S	$T_4N_2M_1$	normal	Azoospermia
L. L.	20	MTU	$T_3N_xM_{1a}$	normal	Azoospermia
M. G.	19	MTU	$T_2N_1M_0$	normal	Azoospermia
M. R.	21	MTU	$T_3N_0M_1$	Atrophy	Severe Oligospermia
N. J.	19	MTT	$T_2N_1M_0$	normal	Oligozoospermia
P. K.	24	MTT + S	$T_3N_xM_{1a}$	Atrophy	Oligozoospermia
D. H.	23	MTU + S	$T_3N_0M_0$	normal	Oligozoospermia
B. E.	19	MTI	$T_2N_0M_0$	Bilateral testicular cancer. Left testicle removed 1974 (MTI)	Azoospermia
M. F.	45	MTU	$T_3N_0M_0$	Atrophy	Azoospermia
H. E.		MTU + S	$T_3N_0M_0$	Left testicle not palpable	Azoospermia

Severe Oligospermia (< 5 million/ml)
Patient M. R. presented with bilateral gynecomastia

Table 2. Plasma concentrations of Testosterone, Oestradiol, Prolactin, LH and FSH in healthy males and testicular cancer patients

	Testosterone (ng/ml)	Oestradiol (pg/ml)	Prolactin (ng/ml)	LH (mIU/ml)	FSH (mIU/ml)
Healthy controls (n = 18)	6.48 ± 2.46	54.84 ± 10.84	9.24 ± 2.89	6.8 ± 3.4	8.4 ± 3.1
Testicular cancer, Beta-HCG not detectable (n = 7)	7.32 ± 1.87	65.52 ± 9.42	10.86 ± 2.03	21.4 ± 8.6	30.2 ± 6.8
Testicular cancer, Beta-HCG > 135 mIU/ml (n = 12)	9.07 ± 3.42	104.86 ± 12.34	12.38 ± 3.84	90.4 ± 16.8[a]	1.4 ± 0.6

[a] LH Ria cross reacts with β-HCG

seminoma. The plasma concentrations ranged from 135.0–2,200.0 miU/ml. In the other cases beta-HCG was not detectable in plasma samples.

2. On clinical examination the volumes of the contralateral testicle appeared to be normal in ten cases. Seven patients presented with atrophy of the contralateral testicle. One patient (B. E.) suffered from bilateral testicular cancer. The left testicle had been removed for MTI in 1974. In another patient (H. E.) the contralateral testicle was not scrotally palpable.

3. In terms of Eliasson's classification semen analyses resulted in normozoospermia in two patients with beta-HCG negative pure seminomas. Oligozoospermia (sperm count < 20 million/ml) was found to be present in six patients and severe oligozoospermia (sperm count < 5 million/ml) in 4. Seven subjects were azoospermic.

4. Two patients whose contralateral testicles were not scotally palpable were evaluated separately. As illustrated in Table 2 a significant elevation of plasma concentrations of oestradiol was found in 10 patients with circulating beta-HCG versus the controls ($p < 0{,}001$) and versus patients with testicular cancers without Beta-HCG production ($p < 0{,}001$). Mean plasma levels of testosterone were elevated in patients with circulating beta-HCG, but this change was not statistically significant ($p > 0{,}05$). Base line LH seemed to be greatly increased in patients with beta-

Table 3. Differences between areas under the curves of i.v. GRF stimulated LH and FSH release

	LH (mIU/ml)	FSH (mIU/ml)
Healthy controls ($n = 18$)	248.3 ± 48.6	196 ± 51.6
Testicular cancer Beta-HCG not detectable ($n = 7$)	499.4 ± 98.7	428 ± 101.2
Testicular cancer Beta-HCG > 135 mIU/ml ($n = 12$)	2,940.6 ± 401.8[a]	98.4 ± 33.8

[a] LH Ria cross reacts with β-HCG

HCG production by the tumour tissue. However, the radioimmunoassay of LH cross-reacts with beta-HCG so that no differentiation between the hormones is possible. FSH appeared to be extremely low in beta-HCG positive patients ($p < 0{,}001$).

5. After GRF load an elevation of LH and FSH was observed in the controls and testicular cancer patients without detectable beta-HCG in plasma samples. Peak values occurred for LH 30–40 min after GRF injection and for FSH 50–60 min following the administration of the releasing factor. In patients with circulating beta-HCG practically no response of LH and FSH to GRF was observed. Areas under the curves of GRF-stimulated LH and FSH were found to be significantly increased in patients with testicular cancers without beta-HCG production versus the controls ($p < 0{,}001$). In patients with circulating beta-HCG a decreased pituitary reserve capacity for FSH ($p < 0{,}001$) was noted (Table 3). Due to cross-reacting radioimmunassay

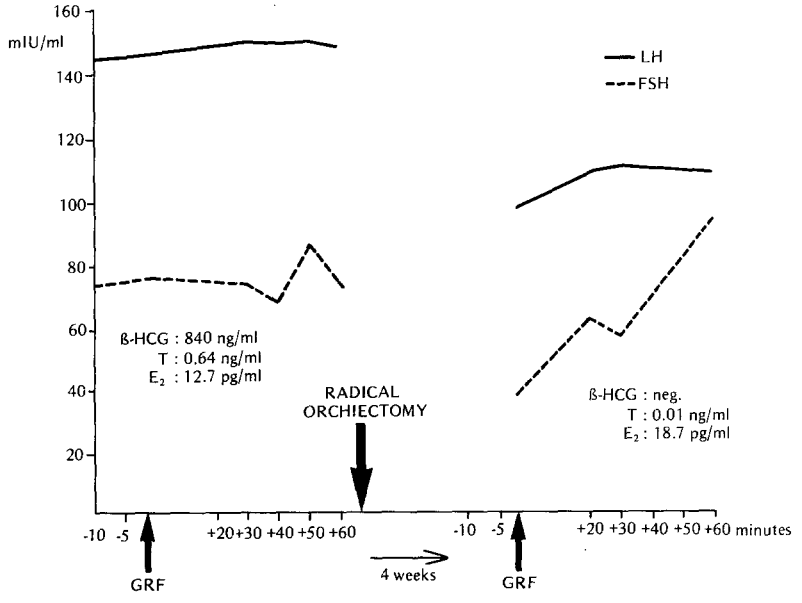

Fig. 1. Endocrine profiles in a patient with bilateral testicular cancer (removal of left testicle in 1974)

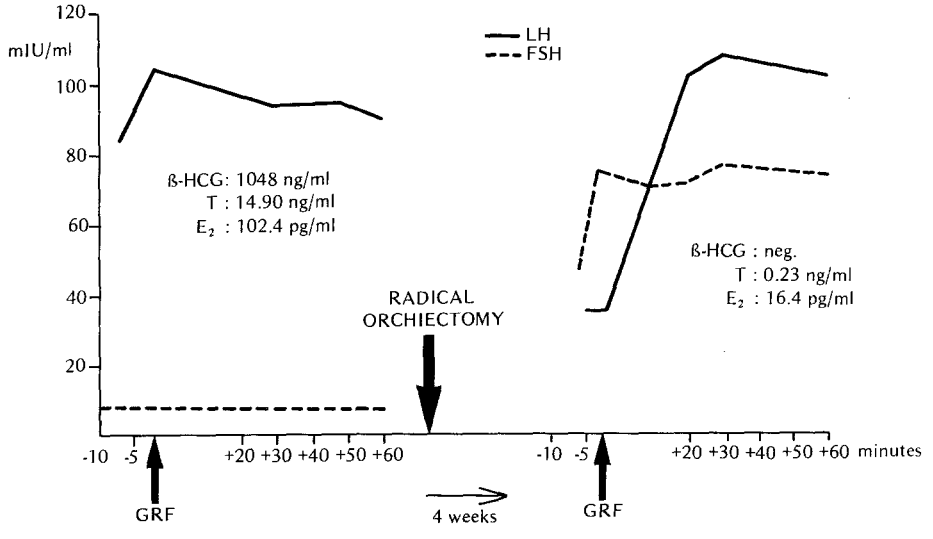

Fig. 2. Endocrine profiles in a patient with testicular cancer and nonpalpable contralateral testis

with beta-HCG the pituitary reserve capacity for LH release was not evaluable.

6. In patient B. E. with cancer in the single testis a level of 840 mIU of beta-HCG was found prior to radical orchiectomy (Fig. 1). Concentrations of LH seemed to be extremely high due to cross-reacting beta-HCG and there was no response to GRF. Plasma testosterone amounted to 0.65 ng/ml and oestradiol to 18.7 pg/ml. The concentration of FSH was extraordinarily high. After removal of the tumour-carrying testicle by radical orchiectomy beta-HCG was not detectable anymore. The base line level of LH was 45 mIU/ml and responded rapidly to GRF with marked elevation.

The patient with a cryptorchid contralateral testicle presented with a level of 180 mIU of beta-HCG before removal of the tumour (Fig. 2). After radical orchiectomy plasma testosterone levels fell from 14.9 ng/ml to 0.13 ng/ml. Beta-HCG was not detectable. LH levels decreased after orchiectomy and showed an exaggerated response to GRF. Base line levels of FSH increased as well as their response to GRF.

Discussion

Testicular function is controlled by hypothalamo-pituitary-gonadal feed-back. Synthesis and release of both gonadotropins LH and FSH are triggered by GRF which is produced in hypothalamic nuclei and transported to the anterior pituitary via the venous portal blood system. By single injection of synthetic GRF the pituitary gonadotropin releasing capacity can be assessed [8, 12]. The action of GRF at the pituitary receptor sites is modulated by testicular function. In hypergonadotropic dysregulation of pituitary gonadal axis an exaggerated response of gonadotropins to GRF can be observed [10, 11]. Oestradiol has been found to suppress the sensitivity of the pituitary to GRF [7, 29].

In patients with germ cell tumours of the testis severe alterations of endocrine profiles concerning plasma levels of oestradiol and gonadotropins can be observed. In patients with beta-HCG producing cancers an increase of circulating oestradiol alters the oestrogen to androgen ratio. The mechanism underlying the development of hyperoestrogenism seems to be activation of Leydig cells in the tumour-carrying and contralateral testicle and interconversion of androgens to oestrogens. Elevated oestradiol is confined to patients with circulating beta-HCG. Patients without detectable beta-HCG in plasma samples did not present with significant alterations of plasma oestradiol versus age-matched healthy controls.

Hyperoestrogenism consequently interferes with pituitary gonadotropin release in terms of inhibition of the secretion of FSH. Base line FSH and response to GRF were found to be significantly decreased. LH levels appeared to be elevated and showed no further response to GRF. However, cross reaction between LH and beta-HCG on radioimmunoassay precludes specific determination of pituitary LH.

In the semi-castrated patient with cancer in the single testis plasma concentrations of oestradiol and testosterone were found to be low despite a remakable production of beta-HCG by the tumour tissue. This can be explained by the fact that Leydig cells in the tumour-carrying testicle have been largley destroyed and further stimulation by beta-HCG is not possible. Corresponding levels of LH and FSH appeared to be elevated as can be found in hypergonadotropic hypogonadism. In the patient with left side cryptorchidism beta-HCG-stimulated plasma testosterone amounted to 14.5 ng/ml which is considered to be above the normal range. After radical orchiectomy the testosterone plasma levels decreased into the castration range indicating that the contralateral cryptorchid testicle was not capable of any endocrine activity. Consequently, pituitary gonadotropins increased and showed an enhanced reaction to GRF.

In patients without beta-HCG production by tumour tissue the hormone profiles were found to be different from those with circulating beta-HCG. Plasma concentrations of oestradiol and testosterone were within normal ranges while concentrations of FSH and LH appeared to be increased and an exaggerated response to GRF was noted. Semen analyses in most of the patients resulted in oligozoospermia or azoospermia. These findings reveal evidence of hypergonadotropic spermatogenetic dysfunction in patients with germ cell tumours of the testis. The increased pituitary release of FSH and LH in oligo- and azoospermic subjects with tubular testicular disorders [10, 17] is explained by decreased inhibin production in the Sertoli Cell. The mechanism underlying spermatogenic dysfunction in germ cell cancers remains a matter of dispute. A high incidence of undetected neoplasia and development of testicular cancer in maldescended testes [15] as well as the frequent finding of carcinoma in situ in testis biopsies of sub- and infertile males [1, 2, 19, 23] support the hypothesis of pre-existing spermatogenetic lesions in many patients with testicular cancer.

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