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The pituitary-Leydig cell axis before and after orchiectomy in patients with stage I testicular cancer

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ABSTRACT

Introduction: This study investigates the pituitary-Leydig cell axis in patients with stage I testicular germ cell cancer (TGCC) followed with surveillance only, in order to evaluate the risk of Leydig cell dysfunction one year after orchiectomy.

Patients and methods: A retrospective evaluation of reproductive hormones in patients with unilateral stage I TGCC ($N = 72$) without relapse diagnosed between 1990 and 2008. A group of healthy males ($N = 706$) served as controls.

Results: Before orchiectomy there were no significant differences in luteinizing hormone (LH) and testosterone (T) levels between human chorionic gonadotropin (hCG)-negative patients and controls, although 33% of the patients were outside the 97.5 percentile when using bivariate LH/T evaluation. At 1-year follow-up there was a significant increase in LH ($\Delta LH = 2.04$ IU/L, $p < 0.001$), and 57% of the patients had an LH/T relation outside the 97.5 percentile.

Conclusion: Patients with stage I TGCC are at increased risk of having an LH/T relation outside the normal range one year after orchiectomy, suggesting insufficient Leydig-cell function. Whether a proportion of these patients will develop manifest hypogonadism and benefit from androgen therapy is yet to be clarified.

1. Introduction

Around 50% of TGCC patients will be cured by orchiectomy alone without further treatment, and the other half will need either chemotherapy or radiotherapy due to disseminated disease.[1] TGCC is highly sensitive to both treatment modalities and most patients will be long-term survivors. This fact has led to an increased focus on long-term complications of TGCC treatment. Several studies have investigated long-term complications of different regimens of chemotherapy and radiotherapy and shown that these treatments cause an increased risk of secondary malignancy,[2] cardiovascular disease[3–5] and changes in fertility and reproductive hormones.[6–11] However, side-effects related to the removal of one testicle without further therapy, has not been critically examined. Removal of one testicle due to TGCC leads to a considerable decrease in the number of the T producing Leydig cells and whether or not the remaining Leydig cells are able to maintain serum T within its normal range on the long term has not been thoroughly investigated. If the Leydig cells fail to compensate for the reduced amount of cells, despite an increased LH drive, manifest primary hypogonadism may evolve and associated conditions like obesity,[12] decreased bone mineral density,[13,14] decreased muscle mass,[15] dyslipidemia[16] and psychological symptoms can develop.[17,18] A recent study has shown that TGCC patients treated with orchiectomy and radiotherapy to the contralateral testicle due to carcinoma in situ were at particularly high risk of developing primary hypogonadism.[19]

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Thus, approximately 60% of patients receiving 20 Gray to the testicle with carcinoma in situ needed androgen substitution in the years following treatment. The majority of patients developed hypogonadism within the first years following treatment, but in some patients, hypogonadism became evident even 5–10 years after therapy.

The aim of the present study was to investigate changes of the pituitary-Leydig cell axis in patients with unilateral TGCC treated with orchiectomy alone in order to detect whether these patients have an increased risk of primary hypogonadism. It has previously been suggested that joint evaluation of LH and T by the use of bivariate charts is a more sensitive expression of the pituitary-Leydig cell axis than evaluation of either of the hormones alone[6,20] and, therefore, this method was used in the present study. Elevated levels of hCG can be observed in both stage I seminomas and stage I non-seminomas before orchiectomy.[21] This can have a significant influence on hormonal levels and for this reason we divided the patients into hCG-positive and hCG-negative groups.

2. Patients and methods

2.1. Patients

Data were extracted from The Testicular Cancer Database at Rigshospitalet, where all subjects with unilateral TGCC stage I treated with orchiectomy and surveillance and diagnosed between 1990 and 2008 were eligible ($N = 436$). In order to compare hormone analyses between patients, we chose to evaluate all patients who had at least one hormone measurement before orchiectomy and one measurement between 6 and 18 months after orchiectomy. If a subject had more than one hormone measurement taken in this time interval, the sample closest to 12 months after orchiectomy was chosen for statistical analysis.

Patients were excluded if any of the following was present: no available hormone measurements before orchiectomy ($N = 245$), no hormone measurements between 6 and 18 months after orchiectomy ($N = 108$), unknown histology, unknown level of hCG at baseline or loss of follow-up ($N = 11$). Thus, 72 patients were included in the study.

2.2. Controls

A cohort of 706 healthy males served as controls in this study and the reference-curves for LH, T and estradiol (E2) as well as the bivariate reference curve for T in correspondence with LH were constructed on the base of this cohort (Figs. 1–3 and 5). In order to obtain age-match between controls and patients, 547 subjects (median age 29 years, range 20–50) were chosen from the cohort for comparison of reproductive hormones at baseline (Table 1). The controls were chosen randomly without prior knowledge of fertility and body mass index (BMI) as described by Aksglaede et al.[20]

2.3. Hormone analyses

Blood samples for hormone analyses were drawn between 8 AM and 12 PM. LH and follicle stimulating hormone (FSH) were measured by time-resolved immunoflourometric assay (DELFIA; Wallac, Inc., Turku, Finland) with detection limits of 0.05 and 0.06 IU/L, respectively. Intra- and inter-assay coefficients of variation (CV) were both below 5% in the LH and FSH assays. Sex hormone binding globulin (SHBG) was measured using time-resolved flouroimmunoassay (DELFIA, Wallac) with detection limits of 0.23 nmol/L, intra- and inter-assay CVs were less than 5.1% for SHBG. Inhibin B was determined using a specific two-sided enzyme immunometric assay from Oxford Bio-Innovation Ltd. (Oxford, UK). The sensitivity of the inhibin B assay was 20 pg/ml, and the intra and interassay CVs were less than 12% and less than 17%, respectively. E2 was measured by RIA (Pantex, Santa Monica, CA (before 1998 distributed by Immuno Diagnostic Systems, Boldon, UK)). The detection limit was 18 pmol/litre, the intra- and inter-assay CVs were less than 8% and 13%, respectively. HCG-β was determined by immunoflourometric assay calibrated against the international standard (WHO75/551) (B.R.A.H.M.S. Kryptor).

2.4. Statistical analyses

Comparison of medians between controls and patients at baseline was performed using Man–Whitney *U*-Test, while paired *t*-test was used for comparing means between baseline and follow-up, except for LH where Wilcoxon Log Rank test was used. *p*-values <0.05 were considered significant.

The reference curves for T, LH and E2 versus age were constructed based on the 706 controls and made by local linear regression smoothing, and similarly the 2.5 and 97.5 percentiles were obtained from smooth variance estimates as described by Aksglaede et al.[20] Bivariate reference charts of T in conjunction with the corresponding LH were constructed based on the 706 controls as described by Aksglaede et al.[20] One can read the 2.5 and 97.5 percentiles of LH and T as the horizontal and vertical lines, respectively. The PC based package of SPSS 17.0 was used for the statistical analyses.

3. Results

Median follow-up time after orchiectomy was 11.2 months, range (6.1–17.5 months). Baseline characteristics of the patients are presented in Table 1.

3.1. LH

At baseline LH was significantly decreased in hCG-positive patients as compared with healthy controls, while there were no significant differences between hCG-negative patients and controls (Table 1). At baseline nine of the hCG-positive patients (82%) had LH levels below the 2.5 percentile, whereas one patient (9%) had LH >97.5 percentile. At follow-up LH had normalised in all patients but four (three with LH levels above the 97.5 percentile). At baseline most hCG-negative patients had normal LH levels (three had LH levels >97.5 percentile (5%) and two (3%) <2.5 percentile). At follow-up, 16 had LH above the 97.5 percentile (28%) and none of the patients were below the 2.5 percentile (Fig. 1). As shown in Fig. 4 there was a highly significant increase in LH between baseline and follow-up in both groups of patients.