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ARTICLE

Increase of Hypophyseal Hormone Levels in Male Head and Neck Cancer Patients

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Head and neck squamous cell carcinoma (HNSCC) develops in at least 80% of cases in men with a history of smoking and heavy alcohol consumption, still it is only diagnosed in a small proportion of alcoholics. Endocrine milieu is an important factor in carcinogenesis and prognosis of several cancer types. The aim of our study was to investigate sex steroid and hypophyseal hormone status of male HNSCC patients in comparison to healthy volunteers and to patients with alcoholic liver disease, to determine possible hormonal alterations characteristic of cancer. Liver function (GGT level), and serum levels of gonadotropic hormones (FSH, LH, prolactin), sex steroids (estradiol, progesterone, testosterone) and sex hormone-binding globulin (SHBG) were compared in 130 male HNSCC patients, 54 patients with alcoholic liver disease but no known cancer, and 56 healthy controls. We found abnormal values of liver function in both HNSCC patients and alcoholics compared to healthy controls, suggesting the presence of alcoholic liver disease in the former group as well. On the other hand, a significant elevation in the level of DHEA, FSH and LH was observed in cancer patients exclusively. As a conclusion, abnormal alterations in sex steroid hormone levels can frequently be found in HNSCC patients, which may be caused in part by the alcoholic liver damage accompanying the disease. The significant increase in FSH and LH serum levels, observed only in the cancer patients, indicates that these hormones may play a role in the development and/or progression of HNSCC. (Pathology Oncology Research Vol 13, No 4, 341–344)

Key words: head and neck cancer, sex steroids, hypophysis hormones, alcoholic liver disease

Introduction

Malignant tumors of the upper aerodigestive tract mucosa, called commonly as head and neck squamous cell cancers (HNSCC), have a well-defined epidemiologic background: over 80% of the cases develop in men with a long history of tobacco smoking, alcohol consumption and poor oral hygiene.[1-8] Consequently, these cancers are commonly accompanied by typical co-morbidities as alcoholic liver disease, chronic pulmonary and vascular diseases, malnutrition and polyneuropathy. Alcoholic liver disease is known to cause abnormalities in the sex steroid hormone status of the patients.[9-12] Disturbance in the hormonal levels can contribute to the development and progression of certain cancers, especially in hormone-dependent organs (e.g., breast, endometrium, prostate), but most probably at other primary sites as well.[13-17] Despite of the clear epidemiological correlation between HNSCC and alcoholic liver disease, no detailed pituitary and sex hormonal status of these patients have been described yet.

The objective of this study was to characterize the hormone status of male HNSCC patients, alcoholic liver disease patients and normal control persons, in order to determine if there were any hormonal changes that are characteristic of cancer rather than the consequence of alcoholic liver disease. In case of cancer-related hormonal abnor-

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malities, further examinations have to prove their possible causal relationship with the development of this type of cancers, their prognostic impact and their usefulness in screening for highly endangered persons in the alcoholic-smoker population.

Patients and methods

Hormonal and liver function data of 240 men were used for comparison in this study: 130 HNSCC patients, 56 healthy control persons and 54 patients with alcoholic liver disease, but no present or past history of cancers of any type. The HNSCC patients included in the study were operated at the National Institute of Oncology for cancer of the oral cavity (n=46), oropharynx (n=31), hypopharynx (n=23) or larynx (n=30). *(Table1.)* The distribution of stages (according to UICC 6th edition) was St I: 5, St II: 26, St III: 36, and St IV: 63 cases. We included only male patients and controls in the study, since the majority of HNSCC patients are men (>80%), and this frequency does not decrease proportionally with the increasing number of smoking and drinking women. Moreover, hormonal levels of women are determined by many other factors (pre- or postmenopausal status, hormonal cycles, etc), therefore, show wide variations, which would make analysis for our particular objective difficult.

To ascertain whether the changes we find are due to chronic alcoholic liver disease as an almost constant comorbidity of HNSCC, or are characteristic of cancer, besides the normal control group we used as second controls a group of chronic alcoholics as well. The diagnosis of alcoholic liver disease in the liver-control patients was based on the clinical history (>5 years history of ≥80 mg regular daily alcohol consumption), and clinical findings (abnormalities in serum levels of hepatic enzymes, ascites, liver biopsy results, spider nevi). Most of the patients had already been treated at hepatology department for their chronic liver disease. The liver function was characterized by the gamma-glutamyl-transpeptidase (GGT) serum level.[18]

Serum levels of gamma-glutamyl-transpeptidase (GGT), sex steroid hormones: estradiol (E2), progesterone (PROG), testosterone (TE), dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHAS), sex hormone-binding globulin (SHBG) and hypophyseal hormones: follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PROL) were assessed before treatment. The free androgen index (FAI) as TE/SHBG was also recorded.

Thirty ml of blood was taken in the morning hours between 8-9 am to avoid uneven results due to daily fluctuation of hormone levels. The blood was centrifuged at 1200 g, and the sera stored at –20 °C until workup. The hormone levels were measured by RIA and IRMA method using the following kits: E2: RIA (Orion Diagnostica, Finland), PROG: RIA (MTAII, Hungary), TE: RIA (Serono, Italy), FSH and LH: RIA (Kabi Pharmacia, Sweden), PROL: RIA (OFJCSSKI, Hungary), SHBG: IRMA (Orion Diagnostica, Finland).

Table 1. **Primary tumor site and stage of the 130 male HNSCC patients**

Site / Stage (UICC 6th ed.)	*St I*	*St II*	*St III*	*St IV*	*Total*
Oral cavity		19	9	18	46
Oropharynx		3	2	26	31
Hypopharynx		3	7	13	23
Larynx	5	1	18	6	30
Total	5	26	36	63	130

The statistical analysis was performed with the BMDP statistical program. The differences between the controls and the patients were analyzed by univariate variance analysis and the Mann-Whitney U-test.

Results

There was no significant difference (p=0.20) in the average age of the healthy controls (50.4±9.3 years), patients with liver disease (50.1±8.5 years) and cancer patients (52.4±9.3 years).

Serum level of GGT was significantly higher in both the alcoholic liver disease and cancer patient group than in controls. The extent of increase was larger in the case of the former group (12.5-fold and 3.1-fold increase, respectively, p=0.0000).

We found significant differences in the levels of all hormones except progesterone, in at least one of the patient groups compared to the healthy controls (*Fig. 1*). Serum levels of SHBG and PROL were significantly increased, while TE and DHAS levels were significantly decreased in both patient groups compared to controls (p<0.01 for all variables). Deviation of the TE and DHAS levels from the controls were significantly higher among patients with alcoholic liver disease than among cancer patients (p=0.0348 and p=0.02, respectively). In the SHBG and PROL levels there was no statistically significant difference in the extent of deviation between the two groups. As a consequence of the decrease in TE and increase in SHBG concentration, free androgen index (FAI) was also lower in both cancer and liver disease patients compared to controls, with no significant variation between the two patient groups. E2 level was found significantly elevated only in the liver disease patients (p=0.0037), while no difference was observed in the case of the HNSCC group (p=0.3188). However, significant increase in DHEA, FSH and LH level was seen in the cancer group exclusively (p=0.0049 and p=0.0003, respectively).

Discussion

The causative relationship between HNSCC and environmental carcinogenesis due to smoking and alcohol consumption is well established. The carcinogenic effect of smoke has been proved, but alcohol itself has never been shown to be carcinogenic itself in laboratory animals.

Chronic alcohol consumption almost always occurs in the history of HNSCC patients, consequently, it must have an important role in the carcinogenesis of HNSCC, other than the direct carcinogenic effect itself. This is also confirmed by the fact that, besides cancers of the upper aerodigestive mucous membrane, primary hepatocellular cancer is also one of the so-called „alcohol-related" cancers.[1,19,20] On the other hand, cancer develops only in a few percent of people who are regular drinkers and smokers, suggesting that other, yet unknown individual characteristics of the future cancer patients must also play a role in the carcinogenesis.[14,19,21,22]

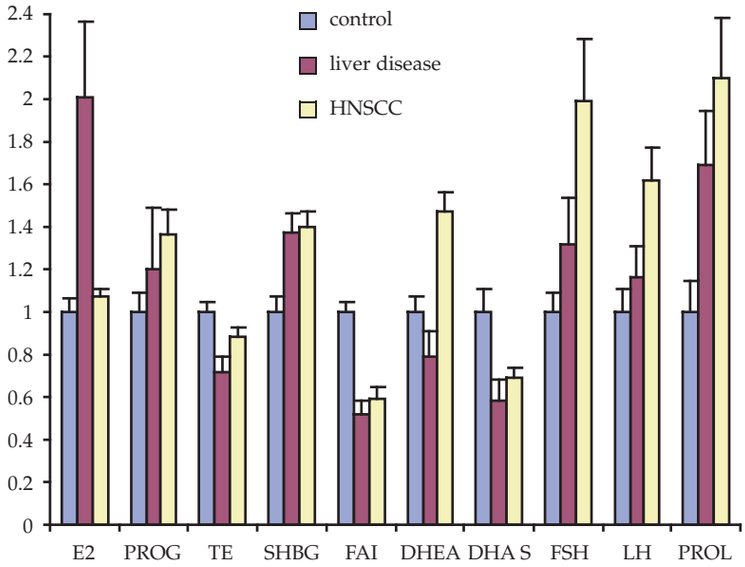

Figure 1. *Hormone levels in male patients with alcoholic liver disease or HNSCC, and in healthy controls. Serum concentrations of hormones are expressed as values relative to mean concentration measured in controls (mean±SEM). Significance of difference vs. control (ANOVA): E2, p=0.0000; PROG, p=0.2852; TE, p=0.0155; SHBG, p=0.0232; FAI, p=0.0000; DHEA, p=0.0006; DHAS, p=0.0089; FSH, p=0.0375; LH, p=0.0112; PROL, p=0.0308*

Our present study, for the first time, analyzed serum pituitary and steroid hormone levels of male HNSCC patients by comparing them with the same factors of chronic alcoholic liver disease patients without cancer and healthy controls. Our aim was to find characteristic differences compared to the controls, which may help in understanding the pathogenesis and improve early detection of this tumor occurring mainly in men.

Our results showed elevated GGT, SHBG, PROL and lower TE and DHAS levels in both patient groups, GGT, TE and DHAS levels being more pathologic in liver disease patients than in HNSCC ones, suggesting that these changes are probably part of the pathologic process leading to alcoholic liver disease. Higher E2 level known as part of chronic liver diseases was found in our liver disease group as well, however, it was not significantly increased in the cancer patients.

Elevated FSH and LH levels compared to healthy male controls were detected only in the HNSCC group, therefore, the changes of these pituitary hormones are characteristic for cancer patients. These results suggest that functional abnormality of the hypothalamus-hypophysis-liver axis might have a role in the development of HNSCC. However, it is noteworthy that these alterations are associated with lower TE and DHAS levels resulting in a relative E2 predominance in male HNSCC patients. Our recent data indicated that HNSCC cells express authentic estrogen and progesterone receptor genes and proteins, suggesting that HNSCC cells may be regulated by sex hormones.[23]

Previous investigations suggest that the development and course of cancers can be influenced by endocrine factors.[13-17,24] Although most of such studies have focused on hormone-dependent tumors, it cannot be excluded that imbalances in the hormonal equilibrium can promote abnormal growth in other tissues as well, which are not hormone-dependent according to our present knowledge. Indeed, a potential role of circulating polypeptides, growth factors and prolactin as tumor markers has been described.[25-27]

The results of this study do not answer the question whether the hormonal changes are simply accompanying the disease, or have a pathogenetic role or prognostic value. Further studies are necessary to discover the exact role of the hypothalamo-hypophyseal hormonal axis in the development or prognosis of HNSCC.

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