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ROLE OF CORTISOL IN THE CARCINOGENESIS OF LARYNGEAL CANCER

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ABSTRACT

Laryngeal precancerosis is a pathogenetic borderline condition including a wide range of risk factors that increase the likelihood of laryngeal epithelial cell malignancy. The induction of tumour growth is without fail associated with the precancerous changes in the mucous membrane of the larynx. Many tumours are hormone-dependent.

The study of the pathogenetic role of hormones in precancerous diseases and laryngeal cancer remains a very relevant problem. Cortisol protects the human body from any stress; however, its role in carcinogenesis is not fully understood. Cortisol is involved in all processes in the body, so almost all cells are equipped with specific receptors. The purpose of our study is to determine the concentration of the cortisol hormone in the blood of patients with laryngeal precancerosis and cancer; to determine its role in malignant transformation and laryngeal carcinogenesis.

The article provides an analysis of the pathogenetic role of cortisol in the genesis of various precancerous diseases and laryngeal cancer. The blood concentration of the stress hormone cortisol was analysed in 56 patients with laryngeal precancerosis and 26 patients with malignant neoplasms of the larynx. The level of cortisol concentration in the blood of patients with laryngeal cancer is significantly higher than in patients with precancerous larynx. Scientific novelty: for the first time, a comparative analysis of cortisol levels in patients with precancerous diseases and laryngeal cancer was carried out.

The results obtained during the research create prospects and generate great interest in studying cortisol receptors in the tumour tissue of the larynx.

KEYWORDS: larynx, hormone, precancerous diseases, laryngeal cancer, cortisol, malignancy, carcinogenesis.

INTRODUCTION

Currently, there are no objective and reliable markers for assessing the risk of malignant transformation of precancerous laryngeal diseases other than determining the degree of dysplasia [Gorban N et al., 2013; Rivera C et al., 2017]. Precancerous and cancerous diseases of the larynx are most often

registered in men over the age of 40-50 years [Antoniv V et al., 2011; Naydyon A et al., 2012]. Women are characterized by an increase in the incidence of dyskeratosis and laryngeal cancer after 51-55 years, or at the age of 40 years. A number of authors associate such findings in this age group with hormonal

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changes in the body [Nazhmudinov I, 2018]. Pre-cancerous and cancerous diseases of the larynx can develop at young age and in childhood [Probst R et al., 2012; Andratschke M et al., 2015].

It has been proven that psychosocial factors can influence the development and persistence of human papillomavirus primarily by affecting the immune response [Chor J et al., 2016; Bates J et al., 2019; Lugović-Mihić L et al., 2021].

The adrenergic pathway and activation of the sympathetic nervous system support carcinogenesis through tumour growth, malignant transformation, macrophage infiltration, angiogenesis, inflammation, spread, etc. Stress hormones (corticosteroids) affect signalling pathways involved in the transformation of malignant cells caused by human oncogenic viruses [Smeets D et al., 2011; Lu D, 2017; Lugović-Mihić L et al., 2021]. It is noteworthy that Th1 cells participate in cellular immunity, release IL-2, IFN- γ and TNF- β and activate macrophages, while Th2 cells stimulate humoral immunity, activate the B-cell response and antibody production, and also promote the secretion of IL-3, IL-5, IL-10 and IL-13.

Back in 1989, Ogoltsova E.S. and Matyakin E.G. demonstrated the results of experiments by various researchers, which indicate that the process of developing laryngeal cancer is hormone-dependent. For instance, experiments involving prolonged lubrication with a benzene solution on the laryngeal mucous membrane of rabbits with altered sex hormone levels (due to castration or extended administration of estrogenic drugs) revealed that papillomas developed later compared to experiments using only a carcinogen [Berstein L, 2000; Zaridze D, 2004].

Kalyi V.V. (2008, 2010) has also studied the pathogenetic role of sex hormones in laryngeal cancer. As a result, it is known that in men with laryngeal cancer, dysfunctions of the pituitary-gonadal system have been revealed both at the level of peripheral endocrine glands synthesizing sex hormones and at the level of central mechanisms regulating steroidogenesis. The nature and degree of severity of the observed changes are associated primarily with the stage of the neoplastic process and with the anatomical localization of the tumour, most often manifested in stage IV lesions of the supravascular larynx [Kalyi V, Chertova N, 2010].

Various stressful events are recognized by the paraventricular nucleus of the hypothalamus,

which participates in a biological chain that combines personal experience, physiological signals and the release of corticotropin-releasing hormone [Iftikhar A et al., 2021]. Corticotropin-releasing hormone influences the pituitary gland, prompting it to release adrenocorticotrophic hormone, which in turn signals the adrenal cortex to release glucocorticoids [Iftikhar A et al., 2021]. Thus, the body's adaptive response to stress depends on many inter-related neuroendocrine, immune, cellular and molecular mechanisms.

The adrenergic pathway and activation of the sympathetic nervous system support carcinogenesis through tumour growth, malignant transformation, macrophage infiltration, angiogenesis, inflammation, spread, etc. Stress hormones (corticosteroids) affect signalling pathways involved in the transformation of malignant cells caused by human oncogenic viruses [Lugović-Mihić L et al., 2021].

The results of research on hormonal changes in people under stress, especially changes in cortisol levels, are also important. Hypocortisolemia is manifested in individuals experiencing severe stress, as well as in those with chronic fatigue syndrome, fibromyalgia, and rheumatoid arthritis. On the other hand, elevated glucocorticoid levels are associated with an increase in white blood cells, a decrease in circulating lymphocytes and in the neutrophils-lymphocytes ratio [Lugović-Mihić L et al., 2021].

Previous studies on corticosteroids in patients with various cancers have indicated the described relation [Magnon C et al., 2013; Lu D, 2017; Iftikhar A et al., 2021]. For example, in patients with prostate cancer, cortisol stimulates carcinogenesis by activating the androgen receptor in the absence of androgens. The findings from the literature review highlight the need for further investigation into hormonal changes in patients with precancerous laryngeal diseases and cancer to enhance our understanding of the role of hormones in carcinogenesis.

MATERIAL AND METHODS

Totally 88 patients aged 25 to 62 years (average age: 55.2 ± 2.08 years old) with malignant neoplasms and precancerous diseases of the larynx were examined. At the first stage of our research, in view of the data of physical examination, complaints, video laryngoscopy results, morphological and histological analysis of the tumours, 56 patients (main group) with precancerous lesions of the larynx were selected from the general cohort,

of which 31 patients have had chronic hyperplastic laryngitis, 10 patients – a polyp of the vocal fold and larynx; leukoplakia of the vocal fold was documented in 8 cases, laryngeal pachyderma – in 7 cases. The comparison group included 26 patients (comparison group) with laryngeal cancer T1-3N0M0G1-3. All patients with a malignant laryngeal invasion had not received any special treatment prior to the examination.

Blood samples for hormone determination in peripheral serum were collected in the morning from the cubital vein, with 10 ml drawn after an overnight fast. The serum was cooled with ice water and centrifuged at 1500 rpm for 10 minutes with cooling no later than 30-60 minutes after sampling. Cortisol levels were measured using an ELISA kit (EIA-1887, Cortisol ELISA) for direct quantitative determination through immunoenzyme assay in plasma. A blood serum sample with endogenous cortisol was incubated in a slot together with an enzyme conjugate. After incubation, the unbound conjugate was washed out with water. The amount of bound peroxidase conjugate is inversely proportional to the concentration of cortisol in the sample. Upon the addition of the substrate, the intensity of colour is inversely proportional to the concentration of cortisol in the sample. This research was conducted at the State Budget Institution of the Ministry of Healthcare of the Czech Republic “Republican Oncological Dispensary”.

RESULTS

The cortisol level was studied in 56 patients of the main group and in 26 patients of the comparison group. Considering that the reference range of cortisol in women and men does not differ, the level of this hormone was assessed jointly by the comparison groups.

It was found that the average concentration of cortisol equal to 577.0 ± 11.1 nM/l (11.5%) in patients with laryngeal cancer was significantly ($p < 0.05$) higher than in the examined individuals with precancerous diseases of the larynx, in whom the average concentration of cortisol was determined to be 528.4 ± 14.2 nM/l. It was also determined that in patients of the comparison group, an increase in the cortisol level was observed significantly more often (11.5%) compared to the main group (5.4%, $p < 0.05$).

DISCUSSION

The presence of markers that correlate with precancerous disease or early stage laryngeal cancer may be crucial for clinical decisions on monitoring

or aggressive treatment of such lesions. To achieve the research goal, several tasks were undertaken: cortisol levels in the blood were measured, and the hormonal status of the patients was evaluated. Additionally, a comparative analysis of cortisol concentrations in patients with precancerous laryngeal conditions and laryngeal cancer was conducted. It should be noted that the average cortisol concentration (577.0 ± 11.1 nM/L) in patients with malignant neoplasms was significantly ($p < 0.05$) higher than that of the examined people with precancerous diseases of the larynx (528.4 ± 14.2 nM/L). Comparison group patients were significantly more likely to have an increase in cortisol levels, compared to the main group (11.5% and 5.4%, $p < 0.05$). The findings can be explained by the fact that the stress-activated hypothalamic-pituitary axis and the sympathetic nervous system act through glucocorticoid and adrenergic pathways that affect immune regulation, including stress-induced immunosuppression, oncogenic infection, as well as other potentially stress-induced neuroendocrine transmitters affecting carcinogenesis (for example, serotonin promotes the growth of tumour cells and angiogenesis; dopamine has the opposite effect) [Lu D, 2017]. A number of authors have provided data on the effect of corticosteroids on carcinogenesis in patients with various types of cancer [Magnon C et al., 2013; Lu D, 2017; Iftikhar A et al., 2021]. We were able to supplement the previously provided data on the relationship between glucocorticoids and carcinogenesis in patients with malignant laryngeal neoplasms.

CONCLUSION

The assessment of the hormonal status, primarily cortisol levels, in patients with precancerous laryngeal conditions and cancer and its connection to the malignant transformation of precancerous diseases of the larynx is of great practical and scientific importance. The data on the role of hypercortisolemia in the process of laryngeal carcinogenesis have been clarified. An increase in cortisol concentration in patients with laryngeal cancer compared with those with precancerous diseases proves the role of cortisol and stress in the malignancy of laryngeal epithelial cells. Patients with precancerous diseases of the larynx are recommended to measure the level of cortisol in the blood. An increase in cortisol levels can be considered a marker of malignancy. The results obtained can be applied to the work of otolaryngologists, endocrinologists and oncologists.

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CONTENTS

4. **STILIDI E.I., KLIARITSKAIA I.L., MAKSIMOVA E.V., MOSHKO YU.A.**
CHRONIC HEPATITIS C WITH CRYOGLOBULINEMIA: FEATURES AND MANIFESTATIONS
10. **ČORIĆ N., BANJARI I., ROLIĆ T., MARIJANOVIĆ I.**
NUTRITIONAL AND HEALTH STATUS OF COLORECTAL CANCER PATIENTS - BASELINE STUDY
20. **AZATYAN V.YU., YESSAYAN L.K., POGHOSYAN M.A., SHMAVONYAN M.V., SAHAKYAN K.T., MURADYAN A.A.**
CHARACTERISTICS OF MORPHOLOGICAL ELEMENTS OF LESIONS OF THE ORAL MUCOSA IN PATIENTS WITH HIV INFECTION
31. **GHAZARYAN H.V.**
THE EFFECT OF THE MEDICINAL COMPOSITION “EFLORNITHINE-ARMENICUM” ON THE PROGRESSION OF THE INFLAMMATORY PROCESS IN AN EXPERIMENTALLY INDUCED AEROBIC WOUND
38. **SHAHBAZYAN S.S., TER-AVETIKYAN Z.A., BADALOVA ZH.E.**
EVALUATION OF KNOWLEDGE AND ATTITUDE REGARDING MORBID OBESITY AND BARIATRIC SURGERY PRACTICE: AN OBSERVATIONAL ANALYTICAL STUDY IN A NATIONALLY REPRESENTATIVE SAMPLE OF ARMENIAN POPULATION
50. **ZILFAYAN A.V., AVAGYAN A.S., MURADYAN A.A.**
THE ROLE OF RESIDENT BACTERIAL-FUNGAL INTERACTIONS IN BIOFILM FORMATION DURING WOUND INFECTIONS: DOES BIOFILM FORMATION IN ECOLOGICAL NICHES CONTRIBUTE TO NORMAL FUNCTIONING IN VERTEBRATE MAMMALS?
61. **MOHAMMED N.D., RAGHAVENDRA R., ARJUN B., AISHWARYA C., SUJATHA B.S.**
EFFECTIVENESS OF THERAPEUTIC PLASMA EXCHANGE IN COMPARISON WITH STANDARD OF CARE IN THE TREATMENT OF YELLOW PHOSPHORUS POISONING: AN OBSERVATIONAL STUDY IN SOUTH INDIAN POPULATION
68. **NAZARYAN L.G., BARSEGHYAN A.B., SIMONYAN M.H.**
CONSUMER BEHAVIOR IN ACUTE DIARRHEA TREATMENT: ANALYZING TRUST IN PHARMACY EMPLOYEES
75. **AGHAHOSSEINI F., OMIDSALAR P., AKHBARI P.**
THE FIRST REPORT OF GRAPHITE TATTOO IN THE SOFT PALATE: A NOVEL CASE WITH A REVIEW OF ARTICLES
81. **BARSEGHYAN A.B., DZOAGBE H.Y., GINOVYAN G.G., NAZARYAN L.G., SIMONYAN M.H.**
ASSESSMENT OF VITAMIN USE AND SELF-MEDICATION PRACTICES AMONG CONSUMERS
87. **KRISTANTO R., JUNITHA K., SUYANTO H., PHARMAWATI M., YUDIANTO A.**
SEX DETERMINATION USING CONFOCAL RAMAN MICROSCOPE WITH CHEMOMETRIC METHOD FROM DENTAL SAMPLE AND CONFIRMATION BY AMELOGENIN GENE
95. **RAPYAN A.A., CHOPIKYAN A.S., SARGSYAN T.M., SISAKIAN H.S.**
COMPARATIVE OUTCOMES FOLLOWING PERCUTANEOUS CORONARY INTERVENTION AND CONSERVATIVE TREATMENT IN ELDERLY PATIENTS WITH ACUTE MYOCARDIAL INFARCTION: SINGLE CENTER RETROSPECTIVE COHORT ANALYSIS
104. **RESTREPO GIL E., AGUIRRE CORREA L.A., CARDONA MAYA W.D.**
KNOWLEDGE AND PERCEPTIONS ABOUT THE DIGITAL RECTAL EXAMINATION: EXPERIENCES IN COLOMBIA
112. **GEKHAEV A.U., ISAKOVA F.S., GADAEV I.SH.**
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