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Patterns of changes in immune and hormonal regulation in hand-arm vibration syndrome and sensorineural hearing loss

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ABSTRACT

The aim of the research was to identify changes in immune and hormonal regulation in patients with hand-arm vibration syndrome and sensorineural hearing loss to substantiate informative biomarkers.

Materials and methods. Men with occupational injury induced by exposure to vibration and noise were examined. The first group included 26 people diagnosed with stage 1 and 2 hand-arm vibration syndrome. The second group consisted of 38 patients diagnosed with sensorineural hearing loss. Serum levels of cortisol, dehydroepiandrosterone sulfate, prolactin, free triiodothyronine (T_3), free thyroxine (T_4), thyroid-stimulating hormone (TSH), and interleukins IL-1 β , IL-8, IL-10 were determined by enzyme-linked immunosorbent assay.

Results. The results of the study revealed the peculiarities in the immune and hormonal regulation in hand-arm vibration syndrome and sensorineural hearing loss. More pronounced changes were observed in sensorineural hearing loss. A common pattern in patients with hand-arm vibration syndrome and sensorineural hearing loss was an increase in cortisol, prolactin and IL-8 and a decrease in free T_4 and IL-1 β . Differences in the identified changes in the immune and hormonal status were characterized by increased TSH production in the first group, and increased free T_3 production and decreased IL-10 in the second group. In hand-arm vibration syndrome, high levels of cortisol were accompanied by a decrease in the IL-1 β and IL-10 concentrations. In sensorineural hearing loss, an increase in the prolactin concentration was accompanied by increased production of IL-8.

Conclusions. The identified features of immune and hormonal relations may be induced by the intensity of cortisol and prolactin production under the effects of various physical factors. Persistent high levels of cortisol and prolactin in the examined patients are important pathogenetically significant factors in the development of the disease. New laboratory indicators (IL-4, prolactin, free T_3) for additional diagnosis of occupational sensorineural hearing loss were identified.

Key words: hand-arm vibration syndrome, sensorineural hearing loss, hormonal status, cytokines, diagnostic markers.

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Закономерности изменений иммуно-гормональной регуляции при вибрационной болезни и нейросенсорной тугоухости

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РЕЗЮМЕ

Цель исследования – выявить закономерности иммуно-гормональной регуляции при вибрационной болезни и нейросенсорной тугоухости для обоснования информативных биомаркеров.

Материалы и методы. Проведено обследование мужчин с профессиональной патологией, индуцированной воздействием вибрации и шума. В первую группу включены 26 пациентов с вибрационной болезнью I–II стадии, во вторую – 38 пациентов с профессиональной нейросенсорной тугоухостью. Методом иммуноферментного анализа в сыворотке крови определяли содержание кортизола, дегидроэпиандростерона сульфата, пролактина, свободного трийодтиронина, свободного тироксина, тиреотропного гормона (ТТГ); интерлейкина (IL) 1β, IL-8, IL-10.

Результаты. Результаты исследования позволили выявить особенности иммуно-гормональной регуляции при вибрационной болезни и нейросенсорной тугоухости. Общей закономерностью у пациентов с вибрационной болезнью и нейросенсорной тугоухостью являются возрастание кортизола, пролактина, IL-8 и снижение свободного (св.) T₄, IL-1β. Различия выявленных изменений в иммуно-гормональном статусе характеризовались для первых усилением продукции ТТГ, для вторых – возрастанием продукции св. T₃ и снижением IL-10. При вибрационной болезни высокие уровни кортизола сопровождались снижением концентрации IL-1β и IL-10, а при нейросенсорной тугоухости возрастание концентрации пролактина сопровождалось увеличением продукции IL-8.

Заключение. Выявленные особенности иммуно-гормональных взаимоотношений могут быть обусловлены интенсивностью выработки кортизола и пролактина при воздействии физических факторов различной природы. Сохраняющиеся высокие концентрации кортизола и пролактина у обследованных являются важными патогенетически значимыми факторами в развитии и течении заболеваний. Определены новые биомаркеры для дополнительной диагностики профессиональной нейросенсорной тугоухости (IL-4, пролактин, св. T₃).

Ключевые слова: вибрационная болезнь, нейросенсорная тугоухость, гормональный статус, цитокины, маркеры диагностики.

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INTRODUCTION

The problem of hand-arm vibration syndrome (HAVS) and occupational sensorineural hearing loss (SNHL) has retained its medical and social significance. These diseases have high prevalence and contribute to the disability of the working population. In this regard, they cause significant social and economic losses, since an occupational disease develops after 5–7 years of contact with the noise and vibration factor. In 3.6% of cases, it is diagnosed in people after 1–4 years of work in conditions of exposure to local vibration [1]. An important role in the pathogenesis of HAVS and SNHL is assigned to nervous, immune and endocrine regulation [2]. It is known that the effects of noise and vibration on the body of workers lead to the state of chronic stress. In this condition, hormones of the adrenal cortex inhibit the activity of cells of the immune system. In the long term, it results in a decrease in the body's resistance to infectious diseases, possible growth of various tumors, etc. [3]. Thus, studies allowing to identify violations of the immune and hormonal regulation remain relevant. In addition, the role of hormones in HAVS and SNHL is not well understood [4, 5]. The findings obtained in the studies may help take necessary measures to preserve health of workers and prevent work-related diseases.

The aim of the research was to identify changes in immune and hormonal regulation in patients with HAVS and SNHL and substantiate informative indicators.

MATERIALS AND METHODS

The study included 64 men with work-related diseases induced by exposure to noise and vibration. The first group included 26 people diagnosed with stage 1–2 HAVS. Their age was 48.9 ± 1.8 years and their occupational contact with vibration lasted 24.2 ± 1.9 years. The second group consisted of 38 patients diagnosed with SNHL. Their age was 54.1 ± 0.1 years and their occupational contact with noise lasted 31.1 ± 1.4 years. Patients were diagnosed by occupational therapists in accordance with the International Classification of Diseases, Tenth Revision (ICD-10). The comparison group consisted of 24 generally healthy men with matching age and employment time, who did not have occupational contact with vibration and noise.

Serum levels of cortisol, dehydroepiandrosteron sulfate (DHEA-S), prolactin, free triiodothyronine (free T_3), free thyroxine (free T_4), and thyroid-stimulating hormone (TSH) were determined by enzyme-linked immunosorbent assay (Alkorbio, St. Petersburg, Russia). The same method was used to measure the levels of cytokines IL-1 β , IL-8 and IL-10 (Vector-Best, Novosibirsk, Russia).

The results were analyzed using STATISTICA 6.0 software package (StatSoft, the USA). The age and employment time of the patients were presented as a mean (M) and a mean error (m). The results of the studies were presented in form of a median (Me) and upper (75%) and lower (25%) quartiles (Q_{25} – Q_{75}). The groups were compared using the Friedman test. Significance of differences was estimated using the nonparametric Wilcoxon-Mann-Whitney test with the Bonferroni correction. Correlation analysis was performed using the Spearman's rank correlation coefficient. The differences were statistically significant at $p < 0.05$. Discriminant analysis was performed according to the manual for physicians "Discriminant Analysis in Biomedical Research" (using STATISTICA 6.1 [8] and the Discriminant Analysis module). The informativity of the analyzed indices was assessed in evaluation steps using the cutoff $F > 3.0$. The Mahalanobis Distance Classification D2 was used as the classification criterion.

RESULTS

We have previously shown that workers with employment experience exposed to vibration have activation of immune cells with the release of IL-1 β and TNF α , which contribute to the production of glucocorticoids [3]. Glucocorticoids can inhibit the immune system. Steroid hormones of the adrenal cortex are regulators of vital processes, such as coordinated growth, differentiation, reproduction, adaptation, and behavior [6]. Based on this knowledge, we conducted a comparative evaluation of the levels of glucocorticoid and thyroid hormones in patients with HAVS and SNHL (Table 1).

The results of the study showed an excess of cortisol in serum of patients with HAVS by 1.7 times ($p = 0.043$) and in patients with SNHL by 2.8 times ($p = 0.0003$), in contrast to the comparison group. A more significant increase in cortisol levels was observed in SNHL patients compared to HAVS

patients ($p = 0.001$). In patients with HAVS, a decrease in TSH level was registered, as opposed

to SNHL patients ($p = 0.00003$) and the comparison group ($p = 0.002$).

Table 1

Hormone levels in patients with hand-arm vibration syndrome (HAVS) and sensorineural hearing loss (SNHL), $Me (Q_{25}-Q_{75})$				
Parameter	Unit	Patients with HAVS, $n = 26$	Patients with SNHL, $n = 38$	Comparison group, $n = 24$
Cortisol	nmol/l	648.7 (278.9–803.6)*	1085.2 (795.1–1296.7)**	378.7 (211.9–532.4)
DHEA-S	nmol/l	1.4 (1.2–1.9)	1.5 (1.1–1.9)	1.7 (1.3–1.9)
Prolactin	mIU/L	117.9 (19.8–184.9)*	254.9 (180.1–297.4)**	55.8 (0.001–109.9)
Free T_3	nmol/l	4.6 (4.3–5.1)	5.4 (3.6–6.4)*	3.8 (3.2–4.8)
Free T_4	nmol/l	11.7 (9.5–12.8)*	13.8 (12.2–14.7)**	15.5 (14.1–16.7)
TSH	mIU/L	0.7 (0.5–1.3)*	1.7 (1.2–2.3)*	1.3 (1.0–1.6)

* differences as opposed to the comparison group; *differences between the groups of patients with HAVS and SNHL are statistically significant at $p < 0.016$.

An increase in the concentration of free T_3 was found only in patients with SNHL ($p = 0.016$). The free T_4 concentration decreased both in patients with HAVS ($p = 0.00001$) and in patients with SNHL ($p = 0.005$) relative to the comparison group. An increase in prolactin concentration by 2.1 times ($p = 0.04$) was detected in patients with HAVS, and by 4.5 times ($p = 0.001$) in patients with SNHL relative to the comparison group. A significant increase ($p = 0.002$) in this parameter was observed in SNHL patients in contrast to HAVS patients. Prolactin is known to stimulate the production of a number of cytokines [7]. A significant prolactin increase ($p = 0.002$) was observed in SNHL patients in contrast to HAVS patients.

The detected hormonal changes in the examined patients were accompanied by cytokine balance disorder (Table 2).

Table 2

Serum cytokine levels in patients with hand-arm vibration syndrome and sensorineural hearing loss, $Me (Q_{25}-Q_{75})$			
Parameter, pg/ml	HAVS, $n = 26$	SNHL, $n = 38$	Comparison group, $n = 24$
IL-1 β	0.01 (0.01–0.1)*	0.01 (0.01–2.7)	0.9 (0.5–1.8)
IL-8	6.8 (5.7–8.3)*	8.7 (4.1–20.5)*	2.7 (1.8–3.1)
IL-4	0.01 (0.01–0.02)	0.01 (0.01–0.01)	0.01 (0.01–8.8)
IL-10	1.1 (0.01–1.66)	0.01 (0.01–0.01)*	2.1 (0.01–13.4)

* differences as opposed to the comparison group are statistically significant at $p < 0.016$.

A significant decrease in the concentration of IL-1 β (0.01 (0.01–0.1) pg/ml, $p = 0.013$) in patients with HAVS and a pronounced trend towards a significant decrease in patients with SNHL (0.01 (0.01–2.7) pg/ml, $p = 0.056$) were revealed. High IL-8 values ($p = 0.002$) were determined in patients with HAVS and SNHL, as opposed to the comparison group ($p = 0.0047$ and $p = 0.0016$, respectively). A decrease in IL-10 was registered in patients with SNHL only (0.01 (0.01–0.01) pg/ml), in contrast to the comparison group [2.1 (0.01–13.4) pg/ml; $p = 0.015$].

At the next stage, the correlation between changes in the hormonal status and cytokine levels was revealed. Following the correlation analysis, it was revealed that patients with HAVS had a negative correlation between cortisol level and IL-1 β level ($r = -0.49$; $p = 0.018$) and a positive correlation between cortisol level and IL-10 level ($r = 0.49$; $p = 0.018$). Patients with SNHL showed a positive correlation between prolactin level and IL-8 production ($r = 0.44$; $p = 0.009$).

Informative indicators for SNHL diagnosis were found with the help of discriminant analysis; 23 immunological indicators were processed from the group of patients with SNHL and the comparison group.

As a result of the calculations, the most significant criteria were IL-4 ($p = 0.0045$), prolactin ($p = 0.0098$), and free T_3 ($p = 0.0227$). The accuracy of SNHL diagnosis equaled 98%.

DISCUSSION

Comparative estimation of glucocorticoid and thyroid hormone levels in patients with HAVS and SNHL revealed both common patterns and distinctive features of their concentration. Both HAVS and SNHL patients were found to have exceeded cortisol levels. In patients with SNHL, cortisol production was 2 times higher than in patients with HAVS. The expected differences in DHEA-S level were not revealed in patients with HAVS and SNHL. It is known that long-term cortisol excess may be accompanied by impaired sensitivity of adrenal cortex cells to adrenocorticotrophic hormone and, consequently, by a decrease in DHEA production. Due to its biological effects, DHEA is considered as an inhibitor to the effects of cortisol on various body systems (especially the immune system and the brain) [8–10].

Individual authors note that there is a decrease in the production of DHEA-S with not changing or slightly increasing level of cortisol in some diseases accompanied by central nervous system (CNS) disorders. It results in a decrease in the DHEA/cortisol ratio [11]. A twofold increase in prolactin level is seen in patients with SNHL compared to patients with HAVS. Prolactin affects the immune system under stress [12], stimulating cytokine production, T-cell proliferation, NK cells, neutrophils, and dendritic cells [13]. A decrease in the average free T_4 and IL-1 β levels and increased IL-8 are a common pattern for both HAVS and SNHL. A specific feature of the detected changes in the patients with SNHL is the increase in free T_3 production and the decrease in IL-10 level. Patients with HAVS are characterized by increased TSH production. As it is known, free T_3 and free T_4 are involved in the regulation of TSH emissions [14]. Free T_3 is the main TSH suppressor, as its high concentrations block TSH production, while low levels increase it [15].

According to the work of R.G. Fedina. et al., there is a significant increase in cortisol and a decrease in free T_3 and free T_4 even in apparently healthy workers exposed to vibration hazards [16]. V.S. Rukavishnikov and A.V. Lizarev demonstrated that only insignificant changes of the mentioned hormones are noted in patients with HAVS along with an increase in the length of service [17]. The results of the examination of workers in the machine-

building industry exposed to increased levels of vibration and noise may be found in literature. The workers showed an increase in adrenocorticotrophic and luteotropic activity of the adenohypophysis and a decrease in androgen production [18].

These results confirm that prolonged exposure to high doses of cortisol and prolactin contributes to the development of various disorders in the immune system regulation [19]. Thus, in patients with HAVS, high cortisol level was accompanied by a decrease in IL-1 β and an increase in IL-10 concentrations. In patients with SNHL, prolactin production had a positive correlation with IL-8 production. IL-1 is a multifunctional cytokine. It easily penetrates the brain through the blood-brain barrier and causes secretion of corticotropin-releasing factor in the hypothalamus. This factor affects the functional activity of the pituitary and adrenal glands. In response to that, the pituitary gland stimulates adrenocorticotrophic hormone secretion. The adrenal cortex stimulates glucocorticoid hormones. There is experimental evidence that cytokines have both immune and neurotropic effects. They are produced in the CNS and can have a direct effect on the nervous system [20, 21].

The established differences in immune and hormonal relationships may be induced by the intensity of cortisol and prolactin production in HAVS and SNHL. The findings prove that high concentrations of cortisol and prolactin in patients with HAVS and SNHL are important pathogenetically significant factors in the development of the diseases. Thus, new informative laboratory indicators (IL-4, prolactin, free T_3) can be used to identify changes in immune and hormonal regulation in patients with SNHL.

CONCLUSION

The patterns of immune and hormonal regulation in occupational HAVS and SNHL were revealed. The common pattern of changes in hormonal and cytokine profiles in patients with HAVS and SNHL was the following: increased levels of cortisol, prolactin, IL-8 and decreased levels of free T_4 and IL-1 β . A distinctive feature of occupational SNHL was the increase in free T_3 production and the decrease in anti-inflammatory IL-10 level. In patients with HAVS, the increase in TSH production was identified. It was found that patients

with HAVS had a negative correlation between the cortisol level and the concentration of pro-inflammatory IL-1 β and a positive correlation between cortisol and anti-inflammatory IL-10. Patients with SNHL had a positive correlation between the prolactin concentration and IL-8 production. The identified features of immune and hormonal relationships may be determined by the intensity of cortisol and prolactin production. Persistent high levels of cortisol and prolactin are important pathogenetically significant factors in the development of HAVS and SNHL. The obtained new informative laboratory indicators (IL-4, prolactin, free T₃) will allow to expand the evidence base for the diagnosis of SNHL.

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