Article

The role of autonomic nervous system imbalance in the pathogenesis of hyperplastic laryngitis

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Abstract: A decrease in the mediator activity of nerve structures in organ tissues leads to the development of neurodystrophic changes and an increase in their sensitivity to certain influences. In these planets, it is important to assess the morphological characteristics of target structures, taking into account the neurodystrophic component of the disease. The aim of the study was to determine the activity of the peripheral adrenergic link of the trophic reflex and assessing the morphological features of the mucous membrane of the vocal folds in chronic hypertrophic laryngitis in patients with neurovegetative disorders. Materials and methods: the study involved 45 patients (37 men and 8 women) aged 23 to 72 years with a diagnosis of chronic hypertrophic laryngitis. An objective study of the upper respiratory tract, a cytological study of reprinted smears from the affected areas of the larynx, a study of the functional state of the ANS, as well as a histological and histochemical study of the removed tissue were carried out. Results. The examined patients were found to have dysfunction of the ANS in the form of insufficient or excessive autonomic support of activity. Morphological signs of keratinization of the epithelium of the mucous membrane of the vocal folds and its active proliferation, as well as dystrophic and atypical changes in cellular elements revealed as a sign of insufficient, tact and a sign of excessive vegetative support of activity. It was found that with insufficient vegetative support of activity, the proliferative activity of epithelial cells is more pronounced than that of a chemer with excess. The same applies to keratosis with atypia and dystrophic changes in the epithelium. Conclusions. The activity of the interstitial adrenergic nerve structures of the mucous membrane of the vocal folds correlates with the characteristics of autonomic activity. The weakening of the processes of synthesis, accumulation and excretion of neurotransmitter is associated with insufficient vegetative support of activity, and their strengthening is associated with excessive. The amount of neurotransmitter in peripheral nerve fibers and endings depends on the nature and intensity of manifestations of neurogenic dystrophies developing in executive tissues – targets of adrenergic innervation.

Keywords: hypertrophic laryngitis, vegetative disorders, adrenergic nerve fibers, neurogenic dystrophy.

Citation: Jurkov A., Alekseeva N., Gordeev D., Sirotkin E. The role of autonomic nervous system imbalance in the pathogenesis of hyperplastic laryngitis. Journal of Clinical Physiology and Pathology (JCPP) 2022; 1 (1): 16-23.

https://doi.org/10.59315/ORLHNP.2022-1-1.16-23

Academic Editor: Valentin Popadyuk

Received: 11.09.2022
Revised: 30.09.2022
Accepted: 16.11.2022
Published: 30.12.2022

1. Introduction

Ideas about the neurodystrophic component of the pathogenesis of various diseases, regardless of their causal origin, appeared as a result of the creation of the doctrine of nervous trophism and nervous dystrophy [1]. They are based on convincing evidence of the role of neural mechanisms in ensuring morphofunctional transformations in the body [1-3].

It has been established that under the action of any pathogenic factor in the body, the trophic function of the autonomic nervous system (ANS) is activated, the state of which determines the course and outcome of a specific pathological process associated with the degree of damage to adaptive, compensatory-adaptive and protective mechanisms [4-6]. The nervous system exercises control over reproduction, growth, development, differentiation of the cell of the organism, the

formation of their communities, the timing of their life and ghibellines [3, 5]. At the same time, the influence of the nervous system on metabolic processes in tissues that are targets of efferent innervation is understood as a trophic function. The weakening of trophic function causes not only dystrophic changes in target structures, spout and cell dedifferentiation in different tissues [2, 3, 7].

To date, it is known that trophic regulation is carried out by reflex [1] and autonomic nerve fibers perform their trophic function with the help of neurotransmitters of the autonomic nervous system (VNS). Such neurotransmitters include catecholic amines: norepinephrine (NA), adrenaline (A), dopamine (DA), indole amine serotonin (CT), acetylcholine (AH), histamine (G), gamma aminobutyric acid (GABA) and others. Among them, the most studied are the neurotransmitters of the sympathetic and parasympathetic divisions of the ANS - NA and AH. A decrease in the mediator activity of nerve structures in the tissues of one or another organ, as well as partial libor complete denervation, lead to an increase in its sensitivity to certain influences [3, 8-10]. This phenomenon is called denervative hypersensitivity [4, 11] and requires its study in the further development of an algorithm for the most effective therapeutic measures. In this plan of materiality, it is also important to identify the morphological features of the target structures, taking into account the neurodystrophic component of a particular disease.

The purpose of this study was to determine the activity of the peripheral adrenergic link of trophic reflexion and to identify morphological features of the mucous membrane of the vocal folds in patients with chronic hyperplastic laryngitis in patients with neurovegetative disorders.

2. Patients and Methods

During the examination of patients who applied to the phoniatric department of the St. Petersburg Research Institute of bump, throat, nose and recited about violations of voice function, in 45 cases (37 men and 8 women aged 23 to 72 years), a clinical diagnosis was made: "chronic hyperplastic laryngitis" In all patients of the former, informed consent was obtained over the expansion of the volume diagnostic measures in comparison with established standards. During the examination, an anamnesis of the disease was collected, a video stroboscopy of the larynx was performed, a cytological examination of smear prints [12] from the mucous membrane of the affected areas of the vocal folds was performed, the functional state of the ANS was assessed using the ANS–spectrum device, whose work is based on the analysis of heart rate variability. Studies of the activity of the ANS were carried out in conditions of complete comfort and determined vegetative tone (VT), vegetative reactivity (VR) and vegetative maintenance of activity (VOD). The results of a similar study on the same device of vegetative parameters in 20 healthy volunteers (15 men and 5 women) were used as benchmarks. Numerical indicators of CIG and hemodynamics obtained in healthy people were taken as control and their changes in the examined patients were taken into account. At the same time, VT was considered normal (eitonia), reduced or increased (hypo – and hypertonus), BP – normal, or increased (hyperreactivity), or reduced (hyporeactivity) and VOD – adequate, excessive or insufficient. These signs are the criteria on the basis of which the functional activity of the ANS is assessed at the system level.

In some patients, hypertrophied areas of the vocal folds had the appearance of tumor-like formations. To correct the voice, these areas were strangled under the control of a video stroboscope, under local anesthesia (10% lidocaine solution), with preliminary premedication with atropine 0.1% and promedol 2%. At the same time, one part of the surgical material was treated according to the traditional histological technique and stained with preparation hematoxylin and eosin in order to make a morphological diagnosis. Another part of the material was used to stage a histochemical reaction. Adrenergic nerve structural was detected by incubating frozen sections in a 2% dissolution of glyoxylic acid (C2H2O3*H2O – glioxylic acid monohydrate 98%, manufactured by the company Fluca A.G., Switzerland), which forms intensity luminescent compounds with biogenic amines in tissues. After setting up the histochemical reaction, the preparation was studied in a luminescent microscope LUMAM-P8 (using a light filter with a free length of 480 nm) and using a photometric nozzle FMEL-1A, the intensity of luminescence (IL) of adrenergic nerve structures was measured, which reflects the degree of their activity.

Cytological preparations were stained according to the hematological method: Maya–Grunwald dye-fixative nao 3 minha was applied to glasses with smears - prints, then it was washed with running water from the back of the glass and the smears were painted according to the Romanovsky method for 10 – 15 min.

Statistical processing of the research results was carried out using Windows 7 software using Microsoft Excel 2010 programs. The Spearman correlation coefficient was calculated, which makes it possible to determine the closeness (strength) and direction of the correlation link between two signs or two profiles (hierarchies) of signs.

3. Results

When collecting the medical history, it was found out that 27% of patients with "chronic laryngitis" had concomitant diseases: bronchial asthma, chronic rhinitis, osteochondrosis, hypertension. Most of the patients had a bad habit of smoking tobacco. All patients complained of persistent hoarseness, some of burning sensation, dryness in the throat. The duration of the disease was: from 2 months to 10 years.

During clinical examination, it was found that the mucous membrane of the vocal folds in patients looked thickened, had a rod bloom, sometimes with a pronounced vascular pattern. Areas of hypertrophy were more often located in the anterior and middle third of one or two vocal folds, had a diffuse or limited appearance. There were signs of keratinization of the mucous membrane (Fig. 1).

During videostroboscopy, all patients had a decrease in the amplitude of vibrations of the vocal folds. The mucous bagpipe was often absent on the side with hypertrophic changes. Non-vibrating areas and areas with signs of leukoplakia were determined.

Figure 1. Videoendoscopic picture of the larynx of a patient with chronic hyperplastic laryngitis

In the study of the functional state of the ANS, dysfunction of the autonomic nervous system in the video of insufficient VOD was found in 35 (77.8%) patients, and excessive - in 4 (8.9%). In 6 (13.3%) cases, adequate VOD supply was provided by increased VT in combination with reduced vegetative reactivity (vegetative dystonia), or increased BP (vegetative hyperreactivity) and vegetative hypotension.

The activity of peripheral adrenergic nerve fibers localized in the mucous membrane of the vocal folds was evaluated using histochemical examination of the surgical material. It showed that in its own plate of the mucous membrane there are adrenergic nerve fibers that are located singly or form fine-grained terminal plexuses with weak luminescence. The luminescence intensity (IL) reflecting the neurotransmitter content inside the adrenergic nerve fiber was 19.6±0.02 rel. units. in varicose veins and 6.6 ± 0.03 rel. units in the intervaricose joints. Such a distribution of IL along the course of the studied fibers indicates their low functional activity and, consequently, a deficit of neurogenic support for the activity of executive tissues at the local level [1]. In excess VOD, a dense network of nerve plexuses of adrenergic nerve fibers with a more pronounced specific luminescence was found (Fig. 2), their IL was 38.35 ± 0.005 relative to food. in varicose veins and 12.7 ± 0.01 rel. units in the intervaricose joints. These signs reflect the activation of the adrenergic link of trophic reflexion and indicate an increased content of neurotransmitter in peripheral nerve fibers.

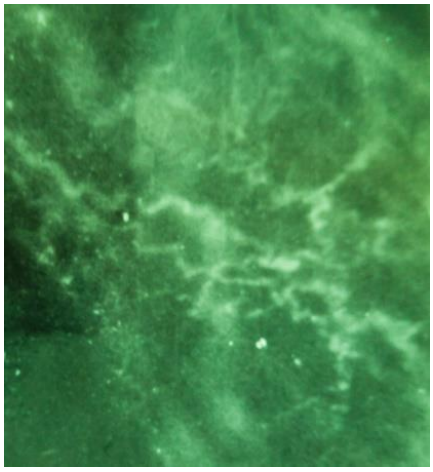

Figure 2. Luminescent adrenergic nerve fibers in the mucous membrane of the vocal folds in chronic hyperplastic laryngitis. The method with glyoxylic acid, (x200)

The close relationship of the functional state of the ANS with the luminescence intensity of peripheral adrenergic nerve fibers was revealed using the Spearman correlation coefficient (p), which was equal to 0.85 at $p<0.05$, to reflect the statistically significant dependence of the IL of adrenergic nerve fibers on the state of the ANS.

With a standard histological examination of the surgical material in all cases, the diagnosis was "chronic laryngitis with focal hyperplasia of the multilayer plateau of the epithelium". The mucous membrane of the vocal folds is a multi-layered carnal non-corneating epithelium that lies above its own plate, consisting of connective tissue. In addition to nerve fibers, it contains numerous elastic connective tissue fibers and blood capillaries. In histological preparations, areas of epithelial proliferation, its excessive keratinization with the focal location of the horny masses on the surface of the epithelial cover and thickening of the epithelial layer due to epithelial hyperplasia were detected. In some cases, flattened cells of the surface layer with basophilic cytoplasm and a large, centrally located nucleus showed signs of metaplasia. Enlarged full-blooded capillaries drew attention to themselves (Fig.3), extensive hemorrhages were also encountered. Circulatory disorders in the mucous membrane of the vocal folds are one of the signs of the inflammatory process. The absence of a granular layer in the epithelial layer and the presence of hyperchromic rod-shaped nuclei in surface cells with compacted basophilic cytoplasm indicated the development of parakeratosis.

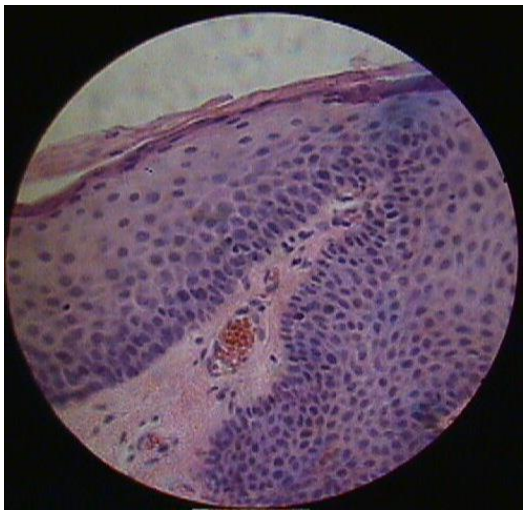

Figure 3. Proliferating epithelium, signs of its keratinization, dilated and full-blooded capillaries in the mucous membrane of the vocal folds in chronic hyperplastic laryngitis. Stained with hematoxylin and eosin. x80

A characteristic feature of the surgical material was the similarity of structural changes in the mucous membrane of the vocal folds with insufficient and excessive water. They reflected the nonspecific reaction of epithelial cells to adverse effects. The differences were mainly related to the degree of severity of these changes.

The same feature was noted in the study of the multilayer plateau of the epithelium found in smears-prints from the mucous membrane of the vocal folds. In cytological preparations, epithelial cells of the superficial elephant predominated against the background of mucus strands, bacterial flora and a small number of cellular elements of inflammation. Signs of keratinization of the epithelium at various stages, its proliferation, dystrophic and degenerative changes were revealed both with insufficient VOD and with excess. With insufficient VOD, the cells of the proliferating epithelium were combined into small layers (Fig.4), groups of 3-4 elements were created, or they were located singly. In the epithelial layers, among the unchanged cells, there were also cells with dystrophic changes, which were represented by moderate morphological rearrangements.

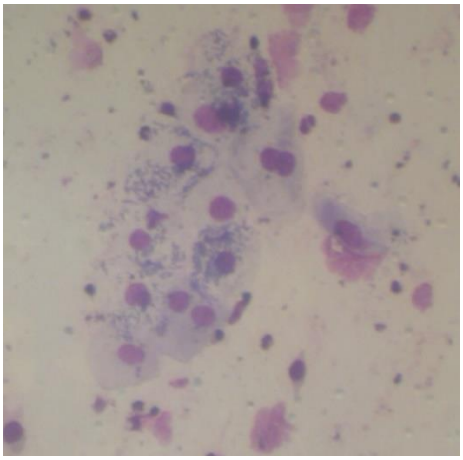

Figure 4. Conglomerate of proliferating epithelial cells in the mucous membrane of the vocal folds in chronic hyperplastic laryngitis. The May-Grunwald fixator with a Romanovsky paint job, (x400)

They consisted in reducing the stainability of the cytoplasm, lightening it, sometimes in vacuolization. In the light basophilic cytoplasm with a small number of inclusions there were hyperchromic nuclei, reduced in size, or, on the contrary, large, rounded centrally located nuclei, the cytoplasmic membrane was practically not visible, so the cell boundaries were indistinct. Epithelial cells with signs of keratinization – with a compacted granular cytoplasm and an elongated hyperchromic nucleus can also be attributed to dystrophically altered cells.

With a particular severity of the phenomena of dystrophy, degenerative changes occur in epithelial cells associated with varying degrees of cell destruction. In the studied preparations, they covered groups of cells containing different amounts of elements and manifested themselves in swelling, loss of basophilia and lightening of the cytoplasm, in which no details were distinguished, except for occasionally occurring vacuoles. The nuclei looked shrunken, hyperchromic, reduced in size, which corresponded to pycnotic changes. Some proliferates consisted of cells with signs of necrosis: the disintegration of nuclei into separate fragments (karyorexis), as well as the "melting" of the cytoplasm and the disappearance of cell boundaries. Proliferates with pronounced polymorphism of cells differing in size and shape, having a more colored cytoplasm and containing large hyperchromic nuclei were detected (Fig. 5). This allows us to judge the presence of signs of cellular atypia.

With increased vegetative reactivity and excessive VOD, the cytological picture was distinguished by the presence of a smaller number of stratified multilayer epithelial plateau, in which cells with dystrophic changes in the cytoplasm, with large, rounded, centrally located nuclei and "blurred" boundaries were located in the middle of unchanged epithelial cells (Fig. 6). Proliferates containing epithelial cells with destructive changes in the nucleus and cytoplasm, they were much less common than with insufficient VOD.

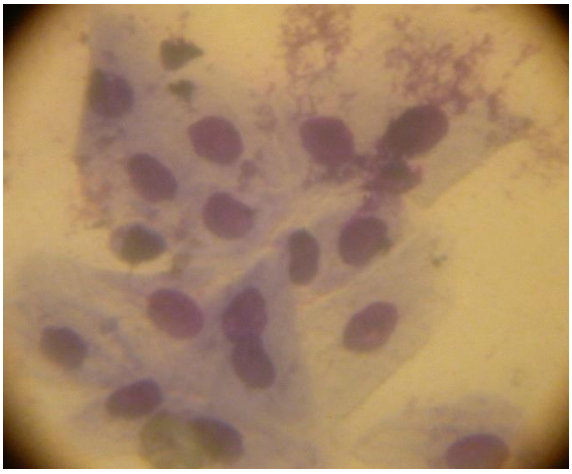

Figure 5. Polymorphism of cells of the multilayered flat non-corneating epithelium in the mucous membrane of the vocal folds in chronic hyperplastic laryngitis. The May-Grunwald fixator with a Romanovsky paint job, (x400)

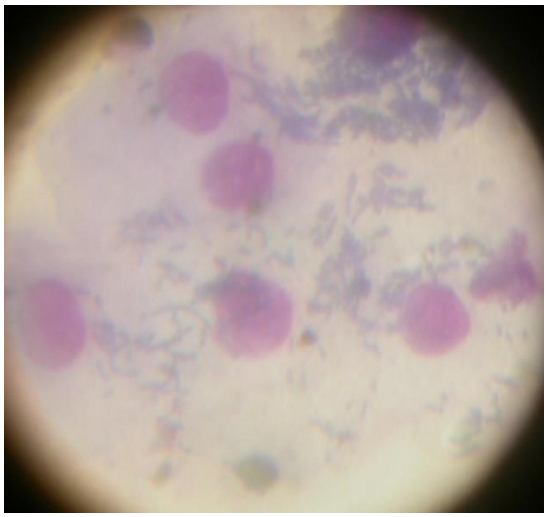

Figure 6. Epithelial cells with dystrophic changes in the cytoplasm and large centrally located nuclei in the mucous membrane of the vocal folds in chronic hyperplastic laryngitis. The May-Grunwald fixator with a Romanovsky paint job, (x900)

4. Discussion

A comparative analysis of morphological changes detected in the mucous membrane of the vocal folds showed that the proliferative activity of epithelial cells is more pronounced with insufficient VOD than with excessive. The same applies to dystrophic and degenerative changes. With excessive VOD, hemorrhages and such severe destructive changes as degeneration of the cytoplasm and the nucleus of epithelial cells, depression to necrosis, were not detected. At the same time, an additional anamnestic farrowing performed during the work process testified to the presence of a clinical picture of peripheral vegetative insufficiency in all patients [3]. Its symptoms include changes in blood pressure and heart rate, cardiac arrhythmias, chest pains, lack of air, fibromyalgia, instability when walking and fear of falling [2, 13-17]. These signs are usually not emphasized by patients and can be detected only with active and purposeful questioning.

Statistical data indicate that the IL of adrenergic interstitial nerve fibers correlates with the characteristics of VOD. At the same time, the weakened processes of synthesis, accumulation and excretion of norepinephrine from nerve fibers are associated with insufficient VOD, and the increased intensity of these processes is associated with excess. However, with increased expenditure of neurotransmitter, the intensity of its synthesis and excretion quickly reaches its maximum and further maintenance of adrenergic nerve structures in a state corresponding to excess VOD becomes impossible. Active diffusion of norepinephrine from nerve fibers and endings leads to

their emptying and contributes to the development of peripheral autonomic insufficiency and neurodystrophic changes in executive structures – targets of adrenergic innervation. Weakening of the processes of synthesis and transport of norepinephrine along vegetative fibers (insufficient VOD) or its excessive consumption (hyperreactivity and excess VOD) with subsequent deficiency of the neurotransmitter are the main neurogenic dystrophies that occur in the larynx and are accompanied by pathological changes in the ultrastructure and biochemical organization of effector cells [7]. Neurodystrophy is involved in the vicious circle of the disease in chronic hypertrophic laryngitis and becomes one of the links in its pathogenesis [1, 6, 18]. In addition, as a result of reduced resistance of the body, neurodystrophy is often the basis for the development of microbial infection. At the same time, chronic inflammation can be secondary, expanding the zones of previously arisen neurodystrophic changes, which include a variety of pathological processes: alteration, up to necrosis, atrophic and vasoparalytic disorders, disorders of proliferation and differentiation of cellular elements [19, 20]. The low content of the adrenergic neurotransmitter in sympathetic nerve fibers with insufficient VOD or its enhanced release from the granule of the content in varicose veins with excessive VOD, followed by a reduction in its reserves in innervation structures, determine the state of tension, and then depletion of the sympathetic end of the ANS up to complete "sympathectomy", when the vegetative provision of protective reactions of the body suffers [11]. In such conditions, disturbances in the regulatory activity of the ANS have a two-phase character: in the first phase, with excessive VOD, arteriole spasm develops with deterioration of blood supply to tissues, protein breakdown increases, azotemia occurs, and foci of dystrophic lesions appear in the target structures. In the second phase, there is a weakening of the vegetative regulation of recovery processes, accompanied by polyvalent hormonal insufficiency, and inflammation in both cases becomes chronic [1, 19].

5. Conclusions

Our own results correspond to the literature data and indicate changes in the functional state of the ANS in patients with chronic hyperplastic laryngitis. These changes manifest themselves at the systemic level as vegetative dystonia and vegetative dysfunction, and at the tissue level as a decrease in the activity of the peripheral adrenergic link of trophic reflection – adrenergic nerve fibers in the mucous membrane of the vocal folds. At the same time, morphological changes are detected in it, which have signs of dystrophy, and in some cases atypia, which allows us to judge the presence of conditions for the development of tumors. Long-term follow-up of the examined patients showed that in three cases there was a malignancy of chronic hyperplastic laryngitis with the formation of squamous cell carcinoma. In general, the results obtained are of great practical importance. They confirm the need to take into account the functional activity of the ANS in patients with chronic hyperplastic laryngitis and turn off measures aimed at correcting neurovegetative disorders in the treatment process.

Acknowledgments.

Author Contributions: Conceptualization, N.A., A.J. and E.S.; methodology, A.J.; validation, E.S.; formal analysis, A.J.; investigation, A.J.; writing—original draft preparation, N.A. and A.J.; writing—review and editing, E.S., D.G.; visualization, N.A.; project administration, A.J. All authors have read and agreed to the published version of the manuscript."

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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