



Influence of selected autoimmunological diseases on phonation devices, diagnostics and treatment

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Markowska D, Jurkiewicz K. Influence of selected autoimmunological diseases on phonation devices, diagnostics and treatment. J Pre-Clin Clin Res. 2023; 17(1): 27–31. doi: 10.26444/jpccr/159126

Abstract

Introduction and Objective. Many autoimmune diseases correlate with phonatory disorders which significantly reduce the well-being and quality of life of patients due to difficulties in verbal communication. The aim of the review is to present the current medical knowledge on ENT complications in patients suffering from selected autoimmune diseases. The text is partially supplemented with the possibilities of diagnosis and treatment of these disorders.

Review Methods. PubMed, PubMed Central, and printed literature were searched using key words related to phoniatrics, larynx, immunology, voice, thyroid and dysphonia. Articles in Polish, German and English were searched. Bibliographies with outdated data and those that did not have the latest update or did not meet the selected criteria were excluded. Exclusions were most often due to an incomplete topic as well as results reported by an unrepresentative group of patients. The review was supported by an additional case study included as relevant to add significant clinical and imaging value to the work.

Brief description of the state of knowledge. Autoimmune diseases are manifested in various body systems, including the phonational system. Both patients and doctors often do not expect that symptoms such as hoarseness, dysphonia, low voice or sore throat may be caused by an underlying disease. The list of ailments, diagnostic options and treatment is intended to present this problem and to increase medical awareness.

Summary. The presented diseases have been shown primarily from the side of disorders in phonation which accompany them. Despite the apparent unrelatedness of the disease with the production of sound, the clinical picture often shows ENT symptoms that are significant for the patient.

Key words

larynx, immunology, tonsil, voice, larynx, thyroid, head and neck surgery, dysphonia larynx, phoniatrics

INTRODUCTION AND OBJECTIVE

Autoimmune diseases are currently quite a significant medical problem due to both their increasing frequency and some difficulty in their treatment. In addition to destructive activities on the tissue from which a given disease originates, autoimmune diseases can cause numerous pathologies of other structures of the organism. Of interest in the course of these diseases are the pathologies of the voice, both in the mechanism of its formation and its output. The review discusses the issues of the phonatory system in patients suffering from autoimmune connective tissue dysfunctions – rheumatoid arthritis and systemic lupus erythematosus, Addison's disease, Graves' disease, diabetes types I and II, and Sjögren's syndrome.

STATE OF KNOWLEDGE

Rheumatoid arthritis. There seems to be an obvious correlation between the incidence of rheumatoid arthritis

and phonation dysfunction, and the illness is caused by the most common failure of the aid mechanism, which is primarily due to action. The main factors supporting the inflammatory process are synoviocytes – cells that are overactive due to pathologically-impaired inhibition functions [17]. Connective tissue autoimmune diseases affect many joints, including those located within the larynx – the annulo-tincture joints. It is worth recalling that the aforementioned joint connects cricoid and tincture cartilage, and that it is an ellipsoidal joint. Inflammatory involvement of this site can be acute or chronic. In the case of acute inflammation, the causes, apart from RA, include gout, acid reflux disease, and a complication after intubation. Patients complain of pain upon swallowing, a feeling of obstruction in the throat, and voice disorders; if the arthritis is bilateral, dyspnoea may occur due to insufficient airway patency at the level of the larynx. Laryngoscopic examination shows swelling and redness of the joint mucosa and restriction of the mobility of the tincture of the cartilage. An important stage in diagnostics is the differentiation of this pathology from the palsy of the recurrent laryngeal nerve. The therapy is mainly based on treatment of the underlying disease causing the joint dysfunction [23–25]. Another related aspect is the pathological asymmetry of the movement of the tincture cartilages, of which their non-linear adduction is of the greatest importance. In 2011, a study was conducted

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Received: 08.09.2022; accepted: 09.01.2023; first published: 17.01.2023

involving 52 people with normal voice and 54 people with voice disorders. Tincture cartilage asymmetry was common in both normophonic and dysphonic speakers, which indicates its possible asymptomatic course. In people with voice disorders, the most common cause of asymmetry was the disappearance of the vocal folds and singing nodules resulting from prolonged and increased incorrect voice emission. The study found that participants had no more left-sided than right-sided asymmetries, compared to those without voice disorders, suggesting a recurrent laryngeal nerve pathway. It is widely believed that the left side of the nerve is more susceptible to damage than the right side because of the longer nerve length – a scroll under the aortic arch [26].

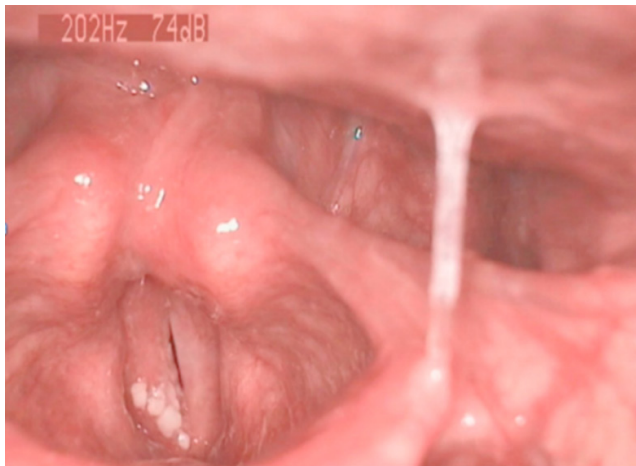


Figure 1. Hyperplastic change in the anterior length of the right vocal fold. According to the VLS assessment, there is no marginal shift along the entire length of the right vocal fold [34]

In a clinical voice study conducted by Koszyła-Hojna B. et al. [1], voice quality disturbances with features of hypofunctional dysphonia were recorded in 43.5% of RA patients. This is confirmed by the results of a study by Roy N. et al. [2], in which about 35% of patients reported complaints with voice. The most common answers in telephone surveys were: 'chronic dry throat' and 'reduced quality of life'. Regarding the exact pathologies, among the pathologies of the larynx. [3], the most common diagnoses were Reinke's oedema (24%), vocal fold hypertrophy (12%) and epithelial lesions (12%). Moreover, half of the patients (48%) showed asymmetry in the movement of the tincture cartilages, and in 38% the inflammatory process was found in the subglottic area. Kirgezen T. et al. [4] presented results showing that in their research group the most common findings were posterior commissure hypertrophy (25.3%) and hyperaemia or oedema of the tincture cartilage mucosa (22.3%). Often there was also thick mucus in the larynx and varicose veins in the vocal cords. In turn, Ferrari de Castro M. A. et al. [5] state that about 70.4% of respondents reported complaints in the area of the larynx. The most common symptoms are periodic dysphonia and the sensation a foreign body in the throat. In 48% of respondents, laryngoscopic changes were confirmed, among which the asymmetry in the movement of the tincture cartilages was again dominant.

Systemic Lupus Erythematosus (SLE). This is also an example of an autoimmune disease that affects connective

tissue. It is not possible to indicate one pathomechanism fully responsible for the emergence and development of this disease. In addition to the obvious autoimmune factor, vascular damage is thought to be involved, which has a particular impact on neuropsychiatric symptoms, and massive production of pro-inflammatory mediators by cells that, as in RA, are not properly inhibited [18]. Similar to RA, pathologies of the phonatory system should primarily affect the joints directly involved in the voice production process. However, the case described by Leszczyński P. et al. [6] draws attention to quite unusual symptoms of SLE. A patient with diagnosed SLE developed severe hoarseness and resistance to pharmacotherapy. On examination, bilateral vocal cord paralysis was found, but no inflammation in the larynx. Electromyography showed impairment of neuromuscular conduction, which finally confirmed and explained the ENT symptoms. At this point, it is worth describing a slightly forgotten, but very important medical problem – paralysis of the retrograde laryngeal nerves. These asymmetrical structures leading from the vagus nerve innervate the vocal folds. One-sided paralysis is manifested only by a slight difficulty in breathing and some difficulty in articulating the vowels formed in the larynx. On the other hand, a serious threat to the patient's life is bilateral paralysis, which causes a narrowing of the gap between the folds, thus significantly reducing the diameter of the airway, causing severe dyspnea. The diagnosis of this pathology is based on an interview, physical examination and, if possible, direct laryngoscopy. Next, imaging examinations are performed – tomography, chest X-ray and ultrasound. [27–30] A valuable test described by Leszczyński P. et al., although available only in larger centres, is laryngeal muscle electromyography which measures with thin needle electrodes the electrical activity of the muscles. This method distinguishes nerve damage from other causes of impaired mobility of the vocal fold. Laryngeal EMG can predict the development of recurrent paralysis of the laryngeal nerve with some probability [31].

According to the current guidelines presented at the World Voice Congress in Istanbul in 2006 and the 7th Pan-European Voice Conference in Groningen in 2007 regarding the treatment of voice disorders, in the case of the rehabilitation of the voice of a patient with laryngeal nerve palsy, this is based on voice emission correction and is based on the close cooperation of an ENT / phoniatriest with a speech-language pathologist trained in voice emission techniques [32].

Similar, equally rare cases have been found and described by Murat O.K. Et al. [7]. Two patients with confirmed SLE had laryngitis. One of them was dominated by voice roughness and loud breathing, while the other patient developed respiratory failure accompanied by chronic coughing as a result of the pathology of the larynx. The course of another, equally atypical case, was illustrated by Cairoli E. et al. [8] in a patient with confirmed SLE who developed hoarseness and a sore throat. ENT examination revealed whitish nodular changes within the tincture cartilage and vocal cords biopsy showed signs of granulomatous lesions. It was shown that the patient had developed histoplasmosis in the larynx.

Addison's disease. Most commonly, the association of autoimmune, primary adrenal insufficiency with cortisol deficiency and symptoms, are closely correlated with its superior role in the organism. It turns out, however, that the unrelated one with phonation, the disease presents several

manifestations in the larynx. In adrenal insufficiency, the voice is quiet and aphonia may occur in the case of hyperfunction of the adrenal glands; the changes mainly concern the female voice and have the features of androphony [9].

Constantly secreted cortisol not only affects the immune system but also increases susceptibility to other diseases which affect the delicate structures and nerve connections, among others, of the laryngeal nerves and the surrounding muscles, which, with a normal short-term cortisol release, have an improved blood supply; however, with prolonged release of this hormone, the homeostasis of the organ is disturbed [33]. This finally provides the answer in the form of the voice disorders observed above. Frequent diagnostics of cortisol levels will allow not only control of the treatment process, but also to improve symptoms related to the phonation apparatus.

Hyperthyroidism. This is also possible due to the very close proximity of the thyroid gland and larynx, as well as the fact that the concentration of individual hormones is reflected in the quality of the voice. The pathomechanism of this disease is based on one of three pathways. Hormones can be released uncontrollably by the thyroid gland, as is the case in acute Hashimoto's disease, or drug-induced amiodarone poisoning. Another possibility is extrathyroidal formation of thyroid hormones, which may occur in goiter or in overdose of oral thyroid hormone replacements. The third path is based on the pathomechanism of an excessive production of hormones by the thyroid gland. This correlates with the activation of the TSH receptor as a result of gene mutation or the presence of autoantibodies. This is the underlying cause of Graves' disease and toxic nodular goiter [19, 37, 38]. It is safe to say that thyroid diseases affect the phonatory apparatus. The neuromuscular form of hyperthyroidism manifests itself, *inter alia*, as myopathy which mainly affects the elderly, more often men. Many muscle groups are involved, including the larynx, with a secondary lesion in the timbre of the voice [10]. Dysphonia is one of the most common symptoms of hyperthyroidism. In the acoustic analysis carried out with the PRAAT software, in which the acoustic features during phonation are assessed in the examined women with hyperthyroidism [11]. From the conducted study, the results of objective measurements showed laryngeal insufficiency and suggested possible pathology of the larynx and dysphonia, of which the most remarkable feature is the low fundamental frequency of the voice [11].

Lejla Junuzović-Žunić et al. [12] examined 27 patients and concluded that hyperthyroidism is mainly the cause of hoarseness or roughness. Often there is a lowering of the voice, tension, and uncertainty about its sound. In 2002, Stojadinovic et al. [13] noted that even in the absence of damage to the laryngeal nerves, transient phonation disturbances may affect up to 80% of patients. Jeannon et al. [14] showed that one in 10 patients undergoing thyroid surgery experience transient voice disorders, and the phonation disturbance will be permanent in one in 25 patients.

Graves' disease (GB) is the most common cause of hyperthyroidism, especially in the 20–40 age group, which is 70–80%. Voice-related problems, as reported in the study, may be temporary or permanent, but may differ in the cause of the problem. During the operation, damage to the recurrent laryngeal nerve may occur, and damage may cause a very wide range of ailments, ranging from

slight changes in the timbre of the voice and hoarseness in the case of unilateral damage to the retrograde laryngeal nerve, to complete silence, dyspnea and stridor (inspiratory dyspnea) when damage occurs to the bilateral retrograde laryngeal nerve – a life-threatening condition which requires a tracheostomy. Another common cause is damage to the outer branch of the superior laryngeal nerve, which results in relaxation of the vocal fold, resulting in a weakening of voice volume which is manifested in the inability to produce high tones, and is especially important for people who work with their voice. Moreover, the timbre of the voice may change [35].

Hypothyroidism. Hypothyroidism, as well as disease-related voice changes, are more common than hyperthyroidism. Different disorders may occur depending on the period of development. If thyroid function is disturbed in childhood, it may cause hearing loss and delay in speech development, which is associated with delayed psychomotor development. A delay in speech development in hypothyroidism is most often caused by swelling of the mucosa in the middle ear, which causes conductive hearing loss, which in turn disrupts the proper sound of the sounds. However, in adults, decompensated hypothyroidism manifests itself in extreme cases with myxoedema, which is the result of the accumulation of large amounts of glycosaminoglycans in the subcutaneous tissue. The most important changes affecting the speech of people with hypothyroidism are thickening of the lips and tongue which make it difficult to articulate correctly. Speech is indistinct and monotonous and additional hoarseness and a dull voice can be observed [23].

Type 1 diabetes. Although many pathologies caused by this disease are widely described, it is worth recalling the mechanism underlying this disorder. Type 1 diabetes is caused by the almost complete destruction by antibodies of the insulin-producing β cells of the pancreas. These are the so-called autoantibodies, produced by the body's immune system, causing autoaggression – the destruction of its own cells. The result is an absolute lack of insulin [39]. In the course of autoimmune, insulin-dependent diabetes mellitus, it can be noted in the study by Dr. Rohit Ravi et al. [15] that 33.3% of the surveyed patients with diabetes reported hoarseness, and 21% tension in the voice. It is also important that people with neuropathy also complained of vocal tension, silence, and hoarseness much more often than people without neuropathy. 40% of the patients complained of the symptoms of acid reflux disease that were causing laryngitis and was observed in most of them. Laiana Weschenfelder et al. [16] came to different conclusions. In their research group of 30 patients with type I diabetes, compared with the same number in the control group, did not observe changes in the self-assessment of the patients' phonatory system. Only those who used insulin infusion pumps complained of pain and throat irritation. In a study of the effect of C-peptide on the process of nociceptive neuropathy in type 1 diabetes mellitus, it turned out that the repair effect of C-peptide on neurotrophic factors and their receptors, as well as on the action of insulin, harmonises with the maintenance of an unchanged axon diameter, and had a beneficial effect on the degeneration of neurons and axons. The presented results explain the mechanisms underlying the clinical improvement of nerve function in patients with type 1 diabetes treated with C-peptide [36].

Sjögren's syndrome (SS). Sjögren's syndrome is a chronic, systemic autoimmune disease caused by disorders of the humoral and cellular response that can potentially lead to a wide spectrum of clinical symptoms [20].

In the pathomechanism of the development of SS, many immunological processes are mentioned, in which numerous immune cells are involved. Among them, an important role in the local inflammatory process is played by T lymphocytes. The destructive effect of cytokines, chemotactic and adhesive factor, as well as the apoptosis process itself, cannot be overlooked [40]. Fatih Ogut et al. [21] conducted a study of the impact of Sjögren's syndrome on changes in the larynx and voice quality. 77 people were examined and their results were compared with 77 people from a control group. It was found that the laryngeal symptoms of SS can affect the adduction of the vocal cords and this may be related to the inability of the strings to sustain periodic vibrations.

In addition to insufficient adduction, other options may also be considered, such as an imbalance in the mass of the two vocal folds. A study by Jenny L. Pierce et al. [22] showed that the incidence of current voice disorder in people with SS was 59.4%. The voice disturbance began gradually, was chronic, and correlated with the severity of SS disease regardless of age, gender, disease duration, co-existing autoimmune conditions, and the use of SS-related drugs. Specific vocal symptoms, including chronic dryness and sore throat, were significantly associated with the severity of SS disease.

Diagnostics. In the case of phonatory system disorders, it is important to start the diagnosis with the primary autoimmune disease because, as described above, a wide range of autoimmune diseases manifestations also reaches the phonation system. Identifying the main cause of the ailments enables the starting of an individual treatment process, thanks to which not only voice-related ailments disappear, but also regression of an autoimmune disease.

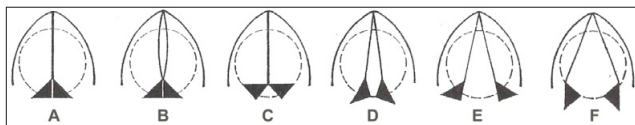


Figure 2. Schematic position of the vocal ligaments and tincture cartilages. A – when completely closed, B – during the articulation of voiced speech elements, C – while whispering, D – while breathing, E – when breathing calmly or at rest, F – when breathing deeply

The following methods are distinguished in diagnostics: perceptual voice assessment, which consists in the auditory assessment of the patient's voice quality, videolaryngostroboscopic assessment, aerodynamic assessment and acoustic examination. There are also voice quality self-assessment polls, such as the Voice Handicap Index (VHI) and V-RQOL (Voice-Related Quality of Life).

Treatment. This is an individual process depending on the assessment of the individual's health condition, causes of the disease or pain, and severity. A wide range of treatments are considered, including patient observation, interventional treatment, surgery, pharmacology and rehabilitation.

Depending on a given disease entity, the treatment process looks slightly different for a different reason. Thanks to the modern very detailed diagnosis of the problem, it is possible to precisely determine the best treatment route.

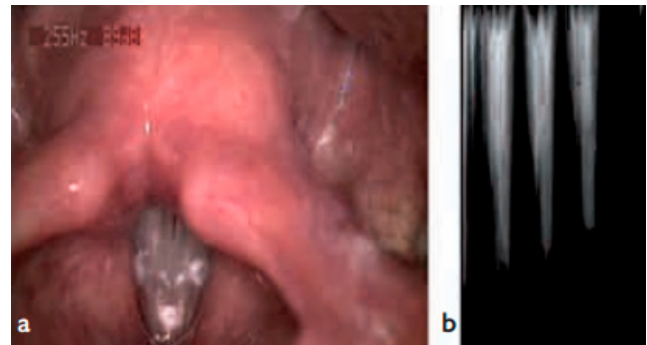


Figure 3. Videostroboscopic image in the glottis closure phase (a) and glottovibrogram (b) showing phonational movements of the vocal folds in a person with a normal voice [37]

CONCLUSIONS

The information collected in the presented review is intended to increase patient awareness and draw the attention of clinicians to the fact that symptoms related to the phonation apparatus may be closely related to a leading autoimmune disease; therefore, symptomatic treatment may not be effective and detailed diagnosis for the primary disease and further treatment should be considered and targeting after identification of the cause of problems affecting the deterioration of the patient's quality of life.

The conclusions resulting from the above review are as follows:

- due to the extensive, heterogeneous structure of the speech apparatus, there are many factors influencing phonation;
- connective tissue dysfunction and the pathologies resulting from it significantly affect the quality of the voice, and thus on the quality of life of patients;
- phoniatric diagnosis should be considered in any patient with autoimmune disease and determine the appropriate selection of diagnostic methods in a specific case;
- in patients with chronic dysphonia, the diagnosis of autoimmune diseases should be considered;
- the implementation of appropriate treatment and rehabilitation can significantly improve the quality of life of patients with autoimmune disease.

Table 1. The most common symptoms and pathological changes appearing in the described pathologies

Pathology	The most common symptoms
Inflammation of the annulo-tincture joint	Reinke's oedema, vocal fold hypertrophy, subglottic inflammation, mucus in the larynx, periodic dysphonia
SLE	Resistant hoarseness, vocal cord paralysis,
Addison's disease	Afonia, androphonia (mainly in women)
Hyperthyroidism	Dysphonia, hoarseness, voice deepening, myopathy
Chronic laryngitis on the basis of GERD	Hoarseness, tension in the voice (using infusion pumps), rapid vocal fatigue
SS	Chronic dryness, sore throat

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