



Work-associated irritable larynx syndrome

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Purpose of review

The purpose of this study is to review the relevant literature concerning work-associated irritable larynx syndrome (WILS), a hyperkinetic laryngeal disorder associated with occupational irritant exposure. Clinical symptoms are variable and include dysphonia, cough, dyspnoea and globus pharyngeus. WILS is a clinical diagnosis and can be difficult to differentiate from asthma. Treatment options for WILS include medical and behavioural therapy.

Recent findings

Laryngeal-centred upper airway symptoms secondary to airborne irritants have been documented in the literature under a variety of diagnostic labels, including WILS, vocal cord dysfunction (VCD), laryngeal hypersensitivity and laryngeal neuropathy and many others. The underlying pathophysiology is as yet poorly understood; however, the clinical scenario suggests a multifactorial nature to the disorder. More recent literature indicates that central neuronal plasticity, inflammatory processes and psychological factors are all likely contributors.

Summary

Possible mechanisms for WILS include central neuronal network plasticity after noxious exposure and/or viral infection, inflammation (i.e. reflux disease) and intrinsic patient factors such as a psychological state. Treatment is individualized and frequently includes one or more of the following: environmental changes in the workplace, GERD therapy, behavioural/speech therapy, psychotherapy counselling and neural modifiers.

Keywords

cough, dysphonia, irritable larynx syndrome, vocal cord dysfunction

INTRODUCTION

The diagnostic term irritable larynx syndrome (ILS) was proposed by Morrison [1] who described a state of chronic laryngeal hypertonicity after repeated noxious exposure and/or postviral infection, wherein subsequent exposure to airborne irritants or triggers results in hyperkinetic laryngeal dysfunction. The nomenclature of laryngeal dysfunction is inconsistent with a lack of consensus on the diagnosis and related clinical features. Examples of the various terms that are used in the literature include laryngospasm, paradoxical vocal fold motion (PVFM), irritant vocal cord dysfunction [2,3] laryngeal hypersensitivity syndrome [4], laryngeal neuropathy, irritable larynx syndrome [1] and many others [3].

The clinical inclusion criteria for WILS [5] are the presence of one or more of the following conditions:

- (1) muscle tension dysphonia
- (2) chronic cough
- (3) episodic laryngospasm (airway obstruction)
- (4) globus pharyngeus.

Patient examination should reveal clinically evident increased laryngeal tension and the presence of a provoking trigger or external stimulus primarily from the workplace. WILS was diagnosed in 10% of patients referred to an occupational lung clinic [5] and were predominantly female (76%) with gastroesophageal reflux disease (GERD) symptoms [1,5]. In the workplace, over 250 agents have been associated with respiratory disorders, with up to 5% of new asthma cases been attributed to occupational exposure [6,7]. Respiratory airborne irritants in the workplace are largely low molecular weight (LMW) particles [8] and common agents are listed in Table 1. The ability of LMW particles to cause harm

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KEY POINTS

- Occupational exposure to airborne irritants is conducive to the development of irritable larynx syndrome.
- Diagnosis of WILS is clinical and strongly supported by laryngeal endoscopy and provocation testing.
- Likely underlying pathophysiological mechanisms of WILS include neuronal plasticity, inflammatory processes and psychological factors.

is more dependent on their physical and chemical properties rather than their ability to provoke an antigen-specific inflammatory response, although some molecules are capable of both processes [9]. There is a spectrum of clinical scenarios that can arise in WILS with varying underlying mechanisms discussed below.

Occupational asthma is the most common lung disease in the workplace. It is important to differentiate WILS in order to avoid unnecessary and unsuccessful treatment in these patients. Treatment of comorbidities and recognition of WILS as a distinct diagnosis from other airway disorders are necessary to manage these patients appropriately.

PATHOLOGICAL MECHANISMS UNDERLYING WORK-ASSOCIATED IRRITABLE LARYNX SYNDROME

The cause of WILS is likely multifactorial and involves both external and intrinsic patient factors [1,4,5,10]. Three main pathophysiological mechanisms have been proposed; neuronal plasticity involves sensorimotor control of the larynx, inflammatory processes (viral infection, GERD) and psychological factors.

Table 1. Common occupational low molecular weight agents

Agent	Occupation/Industry
Cleaning agents	Healthcare, service industry
Anhydrides	Plastics, epoxy, resins
Isocyanates	Urethane, spray paints, foundry workers
Gluteraldehyde, formaldehyde	Healthcare
Ethylenediamine	Plastics, beauty products, rubber
Fumes, exhaust	various
Dyes	Cloth dyeing

RESPIRATORY NEURONAL PLASTICITY AND INFLAMMATORY PROCESSES

The main pathophysiological mechanism proposed in WILS is an alteration of sensorimotor function such that the larynx is in a chronic hyperexcitable state. Further, it was proposed that neural plasticity, a process whereby central neuron response to afferent input is modified, contributes to the development of a chronic hypertonic state and altered responses [1,4]. There is a veritable mountain of research that has emerged from several avenues of investigation regarding neuronal plasticity, much of which is applicable to this clinical diagnosis.

Respiration is largely controlled in the brainstem within the pre-Bötzinger complex adjacent to the nucleus ambiguus in the ventrolateral medulla [11]. Peripheral and central neuronal inputs converge into a central pattern generator to establish basic patterns of respiration. However, the neuronal network is not 'hard wired' and plasticity of synaptic and intrinsic membrane properties occurs [12[¶]]. Nociceptors (C-receptors) in the airways respond to noxious stimuli, which are converted to electrical energy by transient receptor potential-generating channels, further amplified by sodium channels to elicit neuron response.

Neuronal activity can be altered by inflammatory molecules such as prostaglandin E2 (PGE2), which is a product of cyclo-oxygenase-2 (COX2) enzymes and has been shown to inhibit network activity. PGE2 also can directly affect the network generating respiratory rhythms [12[¶]].

Neural plasticity can develop after epithelial and/or neural injury such as workplace exposure to airborne respiratory irritants. Irritant exposure can cause direct epithelial injury that potentially exposes afferent sensory receptors and promotes local production of inflammatory mediators from epithelial cells [7,9]. Epithelial disruption could also facilitate the permeability of chemicals to the sub-mucosa, which is also a site of cellular inflammatory activity and afferent receptors [7,13]. Occupational respiratory irritants are typically of LMW, inhaled as dust or fumes and usually absorbed directly through the respiratory mucosa [8].

The afferent system has several mechanoreceptors: rapidly adapting receptors (RARs) and slow adapting receptors (SARs), which have shown to be abnormal in neuropathic cough and PVFM patients [14]. Modified nociceptors called C-fibres are also present through the respiratory epithelium, which are activated by vanilloids such as capsaicin. Exposure to respiratory irritants (i.e. aldehydes) has been shown to increase the presence of the transient receptor potential vanilloid type 1 (TRPV1) in sensory neurons [15^{¶¶}]. TRPV1 is a capsaicin receptor in upper

and lower airway sensory neurons known to stimulate cough reflex [16] and is also stimulated by smoke exposure.

In a position report on workplace chronic cough, a subset of occupational chronic cough has been attributed to environmental irritant stimuli and propagated by endogenously produced reactive oxygen species and inflammation. Inflammatory cell mediators (i.e. leukotriene B₄) also stimulate the TRPV1 receptor. Neurogenic inflammation occurs when neuropeptides (i.e. substance P, bradykinin) are released in sensory neurons and results in enhanced cough reflex at the sensory receptor level [15²²].

LARYNGEAL CHEMOREFLEX

Investigation into the respiratory control in infants has shown that the laryngeal chemoreflex (LCR) is mediated by modified taste receptors concentrated in the glottic inlet, particularly the inter arytenoid area. The LCR has been demonstrated to be a major protective laryngeal adduction (closure) reflex even in a hypoxic state and modifies to become primarily a cough reflex in older infants and adults. A low chloride or acidic environment stimulates the LCR reflex resulting in apnoea (vocal fold adduction) and swallowing in neonates and in animal models. Respiratory syncytial virus (RSV) infection has been associated with alteration of the LCR function in infants. Cytokines produced secondary to RSV are transported retroaxonally to the brainstem [17]. This is an example of how viral infection can influence central neuron processing.

Research into neuronal plasticity in chronic pain has shown that depending on the dynamic sensory input and network processing, an entirely different output or behaviour can occur given the same peripheral stimulus [18²³]. Chronic noxious stimulation can induce neuronal changes on a molecular, cellular, synaptic and network level. Previous research has shown that superior laryngeal nerve injury is associated with heightened motor reflexes to the thyroarytenoid muscles [19]. Repetitive exposure to a workplace irritant could function as a chronic noxious stimulus of the respiratory afferent system that effects both inflammatory changes and neuron plasticity.

Clinical evaluation of laryngeal sensory motor function has been investigated. A recently developed and a validated self-rated questionnaire (Newcastle Laryngeal Hypersensitivity Questionnaire) was derived from chronic pain and neuropathy literature [20²⁴]. Abnormal sensation was characterized as hypersensory (subthreshold stimuli triggered sensation), paraesthesia (altered sensory information)

and allodynia (stimuli creates a sensation not normally associated). The questionnaire appears useful in not only identifying patients with laryngeal hypersensitivity (to irritant exposure) but also the degree of their symptoms. Other means of clinical testing include cough threshold testing [21] (capsaicin or hypertonic saline provoked) and functional endoscopic sensory testing [14].

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is common in WILS. There is both direct and indirect effect on the upper airway. The well documented laryngo-esophageal reflex is mediated through the vagus nerve wherein mechanical distension or acidic environment in the lower oesophageal stimulated increased laryngeal adductor tone and activity [22]. Direct acidic refluxate exposure on the laryngeal and supraglottic area will provoke laryngospasm (immediate response) via chemoreceptor activation. Chronic exposure can cause oedema, mucosa hypertrophy, contact ulcers and granuloma formation. Vagal sensitization and neurogenic airway inflammation are another consequence of GERD [23]. The typical symptoms include globus, mild dysphagia, throat clearing, chronic cough, increased mucous and dysphonia. GERD is an inflammatory process that initiates the processes described above including neurogenic inflammation.

PSYCHOLOGICAL INFLUENCES

Finally, psychological factors have been identified as pertinent in laryngeal dysfunction disorders. Husein *et al.* [24] reported on formal psychological testing in 47 PVFM patients (not all irritant based) using the Minnesota Multiphasic Personality Inventory 2 (MMPI-2) and Life Experience Survey to evaluate stress. There was an increased value on the hypochondriasis scale and a mild elevation on the depression scale compared with normative data. Elevated levels of negative life stress were found in the female participants. Classic conversion disorder pattern was found in 38% of individuals. Interestingly, 25% had no psychopathology identified. PVFM was associated with GERD (78%) and past psychological history was present in 50%.

A systematic review of the literature investigating any psychological intervention for VCD was reported by Guglani *et al.* [25]. Of 2944 publications relating to VCD in the past 50 years, 16 publications were identified as meeting their criteria. Treatment recommendations are based largely on case reports or small series. It often involves multiple modalities such as formal psychotherapy, behavioural therapy with

speech disease, biofeedback and antidepressants. All of the aforementioned were found to be useful in certain subsets of patients. The authors concluded that psychotherapy has a role to play on an individual basis.

CLINICAL EVALUATION OF WORK-ASSOCIATED IRRITABLE LARYNX SYNDROME

WILS is a clinical diagnosis and an excruciatingly detailed history and timeline of symptoms are key components of the evaluation. A negative methacholine challenge or a clinical history inconsistent with asthma and/or a lack of response to asthma therapy often prompts the referral to an otolaryngologist for further assessment. Symptoms are often dose dependent and onset is immediate (seconds to minutes) after exposure to an airborne irritant or trigger. One or more of the following symptoms can occur: dysphonia, cough, globus or dyspnoea [1,4,5]. Mucous production and irritation as well as a sense of blockage at the throat are typical symptoms [4]. Improvement is noted outside the workplace, although the episodes frequently evolve over time with patients experiencing symptoms when exposed to any strong odour or irritant and common household products such as perfume, smoke and cleaning solutions. Exercise and voice use are other triggers that may occur. Not infrequently, individuals also experience dermatologic, ocular or nasal symptoms such as tearing, rhinitis, post-nasal drip and skin rash [8].

WILS patients have often been at their present occupation for a lengthy period and an unusual combination of environment and/or patient conditions occurred at the onset of these symptoms [5]. Environmental factors such as a chemical spill, new irritant presence, poor ventilation and other air quality conditions (humidity, heat) may heighten irritant exposure.

These processes are distinct from the immune-mediated primary asthma and clinical presentation is also distinct, although up to 30% of patients with ILS/WILS will also have asthma [1,5].

Functional inquiry should also include symptoms of GERD, atopic history and past medical history of laryngeal or respiratory disorders. Response to previous treatment such as nebulizers, inhaled or systemic steroids or workplace changes is also useful. Dual probe pH with oesophageal manometry testing may be indicated to evaluate reflux disease particularly if patients have persistent symptoms despite medical therapy.

Other means of testing laryngeal sensation include hypertonic saline challenge, functional

endoscopic evaluation with sensory testing and cough reflex sensitivity testing (i.e. capsaicin), which are done primarily in a research setting.

Investigations for these patients include referral to a respirologist and/or occupational medicine specialist clinic if not already carried out. Skin testing, spirometry and frequently methacholine challenge is carried out to evaluate for allergic disease and asthma [2,5]. Spirometry testing can be normal, or during an episode of laryngeal adduction causing airway obstruction, a truncated or flattened inspiratory limb can be seen on a flow volume loop. At our institution, patients identified as possible WILS patients are evaluated in a multidisciplinary setting with a laryngologist and speech language pathologist. Detailed history, vocal cord dysfunction, VHI (voice handicap index) and reflux symptom questionnaires are collected and physical examination is conducted.

Clinical assessment at the Voice Disorders Clinic includes neck examination, naso-endoscopy and indirect laryngoscopy with or without provocative testing. Neck palpation and observation during phonation and respiratory tasks are done to ascertain the presence of increased tension in the extrinsic laryngeal muscles (cricothyroid, thyrohyoid and so on).

As in muscle tension dysphonia, signs of increased laryngeal tension such as supraglottic hyperfunction, hyperradduction and exaggerated posterior glottic gap are frequently observed [1,2,10]. A variety of respiratory tasks are observed, including normal 'at rest' breathing, deep inhalation, forced exhalation, sniffing, panting and pursed lips exhalation as part of the protocol with video endoscopic documentation. Provocation testing is done after appropriate consent in a well tolerated environment (acute care hospital), with a speech language pathologist and physician present under video endoscopic monitoring. Patients are asked to report symptoms during inhalation of various chemicals such as perfume, hand sanitizer, and cleaning solution or a sample of the specific occupational trigger if available. An abnormal provocation test may include the following laryngeal hyperkinetic responses: inappropriate vocal fold adduction during inhalation or early exhalation, supraglottic hyperfunction, increased posterior tongue base movement, repeated swallowing and coughing. Increased mucous production may also be observed.

The position of the folds may include variable degrees of adduction during inhalation and/or early exhalation with a convex shape of the vocal folds and an exaggerated posterior glottic gap. The diagnosis of ILS is clinical; however, observation of

laryngeal hyper-responsiveness after exposure to a triggering irritant is strongly supportive of the diagnosis.

Voice changes are usually immediate with breathy strained, pitch and phonation breaks or complete aphonia.

Frequently, if the individual becomes symptomatic, behavioural therapy may be trialled during the same session.

TREATMENT

Given that irritant exposure is primarily or only associated with the workplace, avoidance of irritant exposure is an important part of treatment for this disorder. Engineering (i.e. ventilation) or location changes should be done at the workplace to prevent or minimize exposure to specific irritants. At times, personal protective equipment has been helpful in the workplace such as a particulate or vapour respirator (mask).

Often escalating asthma therapies have been instituted and have been unsuccessful in managing patient symptoms. Given the high degree of GERD symptoms and/or findings on laryngoscopy, medical therapy is appropriate in these patients. Proton pump inhibitor is the mainstay of treatment currently. Treatment of any associated and aggravating issues such as rhinosinusitis and allergic rhinitis (i.e. steroid nasal spray) is also offered if it has not been done prior to evaluation. If evident from the history, referral for psychotherapy or counselling may be indicated.

ILS patients can realize significant improvement from behavioural therapy with an experienced speech language pathologist. The focus of therapy is on reframing process with the identification of behaviour or respiratory patterns to be changed and develop adaptive strategies [1,4,5,10,14]. Cognitively, the patient receives education on their condition and the respiratory or voice tasks that may help. Biofeedback is helpful particularly using video endoscopy. Relaxation techniques, both focal and generalized, are helpful to reduce muscle tension. Specific respiratory retraining techniques are helpful as well.

Given the postulated underlying mechanisms of altered central neural network control of the larynx, neural modifiers have been used to treat WILS and associated conditions. Gabapentin and pregabalin have both been used to treat chronic cough and irritant VCD [26,27]. A double-blinded randomized trial on chronic cough (neuropathic cough) demonstrated that patients had significantly reduced cough while on gabapentin compared with placebo [26]. Gabapentin contributes to remodelling of

synaptic contacts and inhibits excitatory synaptogenesis [18*].

CONCLUSION

ILS is a condition in which dramatic laryngeal hyperfunction can occur after exposure to a trigger or stimulus. In an occupational setting, this condition has been associated with respiratory irritants that are capable of inducing airway hyperresponsiveness through nonallergic mechanisms. The cause of ILS is believed to be multifactorial and results in a persistent hyperreactive state of the peripheral and central neuronal control of laryngeal responses to sensory stimulation. Diagnosis requires a careful, detailed history and clinical evidence of increased laryngeal tension. Provocation testing is helpful in order to observe abnormal laryngeal hyperkinetic activity during respiratory and phonatory tasks. Neural modifiers may be beneficial in this patient population.

Management strategies include avoidance of irritant exposure, patient education and behavioural therapy as well as medical management of associated comorbidities such as GERD, rhino sinusitis, psychological factors and coexisting asthma. Given the proposed underlying mechanisms involved in WILS, neural modifiers such gabapentin and others may also prove to be helpful in this patient population. Randomized controlled trials are necessary to investigate the efficacy of this modality of treatment. Treatment goals are to control or reduce symptoms, avoid unnecessary therapies and return the individual to the workplace if possible.

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Conflicts of interest

No conflicts of interest to report.

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- of special interest
- of outstanding interest

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