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The Irritable Larynx Syndrome

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Summary: Muscular tension dysphonia, episodic laryngospasm, globus, and cough may be considered to be hyperfunctional laryngeal symptoms. Suggested etiological factors for these symptoms include gastroesophageal reflux, psychological problems, and/or dystonia. We propose a unifying hypothesis that involves neural plastic change to brainstem laryngeal control networks through which each of the above etiologies, plus central nervous system viral illness, can play a role. We suggest that controlling neurons are held in a "spasm-ready" state and that symptoms may be triggered by various stimuli. Inclusion criteria for the irritable larynx syndrome are episodic laryngospasm and/or dysphonia with or without globus or chronic cough; visible or palpable evidence of tension or tenderness in laryngeal muscles; and a definite symptom-triggering stimulus. thirty-nine patients with irritable larynx syndrome were studied. Gastroesophageal reflux was felt or proven to play a major role in a large number of the group (>90%), and about one third were deemed to have psychological causative factors. Viral illness seemed quite prevalent, with one third of patients able to relate the onset of symptoms to a viral illness that we feel might lead to central nervous system changes. Our proposed hypothesis includes a mechanism whereby acquired plastic change to central brainstem nuclei may lead to this form of hyperkinetic laryngeal dysfunction. It gives structure and reason to an array of therapy measures and suggests direction for basic research. **Key Words:** Muscular tension dysphonia—Laryngospasm—Vocal fold dysfunction—Paradoxical vocal fold motion adductor breathing dystonia—Globus—Chronic cough—Gastroesophageal reflux—Spasmodic dysphonia—Neural plasticity—CNS viral illness—Irritable larynx syndrome—Environmental sensitivity.

Hyperkinetic laryngeal dysfunction presents in numerous forms:

Muscular tension dysphonia (MTD) may manifest as vocal fry, characterized by anteroposterior (AP) compression, phase asymmetry, low pitch, diplophonia, and rough voice quality; laryngeal isometric posturing characterized by AP compression, exaggerated posterior glottic chink, lateral compression in the membranous vocal folds, low pitch, and breathiness; or a general hyperadducting pattern characterized by glottic (and supraglottic) compression, adduction spasms, and strained voice quality. Voice use may be accompanied by laryngeal pain and fatigue. In some patients the dysphonia is ascribed to psychological cause and termed "psychogenic" or

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"functional." In others it is attributed to technical, postural, or behavioral misuse. Since the neuropathology causing the symptom is not understood, our hunches and experiences of what seems to work in most cases guide therapy. We originally described MTD[1] in 1983, and subsequently presented works on diagnostic criteria,[2,3] pattern recognition,[4] a pathophysiological model,[5] and phonatory function characteristics for muscle misuse dysphonia.[6,7]

Episodic laryngospasm, vocal fold dysfunction, paradoxical vocal fold motion, and adductor breathing dystonia are all descriptive terms that relate to a situation in which the glottis closes down in such a way as to inhibit airflow. If one reads the psychiatric literature one would be likely to class "vocal fold dysfunction" as a somatoform disorder or possibly an anxiety disorder, and believe that "speech therapy" or psychotherapy is most likely to help.[8,9] Respiratory physicians may relate "paradoxical vocal fold motion" to asthma and treat it as such with inhaled or systemic bronchodilators and steroids. The respiratory literature is replete with articles distinguishing vocal fold dysfunction from asthma but tending to leave the etiology as "functional".[10-13] Neurologically focused clinicians may decide that the breathing problem is a variant of focal laryngeal dystonia and recommend intracordal injections of botulinum toxin. Others of us may feel the laryngospasm is due to gastroesophageal reflux (GER) and are determined that the problem will resolve with long-term proton pump inhibitors.[14-16] Reports in the pediatric literature relate GER to laryngospasm as well as sudden infant death syndrome.[17]

Are these really four different disorders? If not, which is "real"?

Chronic cough, throat clearing, and the sense of a lump in the throat (globus pharyngeus) are also symptoms that may be tied to muscle tightness in the laryngeal area. They have been attributed to respiratory disease, GER,[18] psychological stress,[19] and allergy among other things.

While the larynx usually looks structurally normal in patients who complain of these symptoms, we have become increasingly aware of other physical findings that are probably important, including abnormal laryngeal posture and palpable muscular tension in and around the larynx. Aronson[20] described this a number of years ago. Harris and Lieberman[21] and Roy and Leeper[22,23] have added further detail, using manipulation techniques to reduce laryngeal tension and reduce symptoms.

Some patients complain of variants of laryngospasm or dysphonia, or both, and their symptoms are triggered by something definitive. Triggers may include environmental stimuli such as odors, airborne particles, or chemicals. Foods, refluxate, esophageal stimuli, or voice use and/or coughing may trigger symptoms. When they also have visible or palpable evidence of laryngeal muscle tension they are suffering from the irritable larynx syndrome (ILS).

In this article we present a summary of clinical information about 39 consecutive patients with ILS, and propose a unifying neuropathological hypothesis.

METHODS AND MATERIALS

This study is based on collection of clinical data from patients attending the Pacific Voice Clinic at the Vancouver General Hospital and University of British Columbia between September 1996 and December 1997. Data from all patients who had been given the ILS label during this time were collated to include subject identity, symptoms, physical signs, possible causes, symptom triggers, and treatments given.

We define the irritable larynx syndrome as hyperkinetic laryngeal dysfunction resulting from an assorted collection of causes in response to a definitive triggering stimulus.

Inclusion criteria for ILS diagnosis are as follows:

1. Symptoms attributable to laryngeal tension
   - dysphonia and /or laryngospasm
   - with or without globus and/or chronic cough
2. Visible and palpable evidence of tension
   - laryngoscopic lateral and AP contraction
   - palpation: SH, TH, CT, pharynx
3. Presence of a sensory trigger
   - airborne substance, esophageal irritant, odor

The ILS diagnosis is excluded if there is apparent organic laryngeal pathology, an identifiable neurological disease, or an identifiable psychiatric diagnosis.

RESULTS: 39 CONSECUTIVE PATIENTS WITH ILS

Patients given the ILS diagnosis tend to have complex combinations of symptoms, signs, and background factors. To help us sort the data in a meaningful way we began by considering groupings based on (a) symptom complex, (b) triggering stimulus, (c) etiological possibilities, and (d) treatments provided.

Symptom complex groupings

Laryngospasm and dysphonia are the 2 major ILS symptoms, with the former being the most distressing. "Minor" symptoms include globus, chronic cough, and perilaryngeal pain. The following list shows the number of patients in each of 5 symptom groupings (**L**aryngospasm, **D**ysphonia, **G**lobus, **C**ough, **O**ther).

L: Laryngospasm alone (5)
L/O: Laryngospasm with D, G, or C (20)
D: Dysphonia alone (4)
D/O: Dysphonia with L, G, or C (6)
O: Other (G and/or C) (4)

It is noted that 26 patients had dysphonia or laryngospasm in combination with other symptoms. Since airway compromise is more distressing than voice loss, most patients will be included in the laryngospasm group when both are present. Table 1 shows the age and sex demographics for these 39 patients.

The physical signs that seemed to have greatest importance were each graded on a 0 to 3 scale, where 0 was normal, 1 mild, 2 moderate, and 3 severe. Posterior laryngeal inflammation, AP supraglottic compression, and lateral glottic compression were judged from videoendoscopic examination. Tension in suprahyoid, thyrohyoid, cricothyroid, and pharyngeal constrictor muscle groups was assessed by palpation. Table 2 shows the averaged severity of each of the rated physical signs for each of the 5 symptom groups.

TABLE 1. *Thirty-nine Patients With ILS: Demographics*

	L	L/O	D	D/O	O	Total
Total patients	5	20	4	6	4	39
Male	1	2	0	2	1	6
Female	4	18	4	4	3	33
Age range	33–64	23–66	39–68	34–70	46–69	
Avg. age	50	46	52	55	55	

Note: L = laryngospasm; D = dysphonia; O = other (globus/cough).

TABLE 2. *Averaged Physical Sign Severity*

	L	L/O	D	D/O	O	Total
Total patients	5	20	4	6	4	39
Posterior inflammation	1.6	1.1	0.7	0.8	1	1.1
AP squeeze	1.2	1.5	1.7	1.5	0.3	1.4
Lateral squeeze	1.4	1.1	1.5	1.6	0.3	1.2
Suprahyoid tension	2.2	2	2.5	2.3	1.5	2.1
Thyrohyoid tension	2.2	2.3	2.7	2.5	1.7	2.3
Cricothyroid tension	2	2	2.5	2.1	1	1.9
Pharyngeal tension	2	1.6	1.7	1.8	1	1.6

Note: 0 = normal; 1 = mild; 2 = moderate; 3 = severe.

Table 3 itemizes the triggering stimuli that were identified by patients in each of the symptom complex groups. Airborne irritants and GER were mentioned most frequently, followed by perfume, foods, emotion, and voice use. There were no significant differences in trigger incidence among the various groups. Possible etiologic factors that could have led to the development of symptoms were considered for each group and the results are shown in Table 4. The overwhelming presence of GER, proven or highly suspect, is obvious. It is interesting to note that almost half of the patients were able to relate the onset of symptoms to a well-recognized viral illness. Of 17 viral illnesses only 5 were upper respiratory infections. There were 3 flulike illnesses, 2 herpes zoster infections, 2 with viral meningitis, 2 Epstein-Barr infections, 1 Lyme disease, 1 tick-borne infection, and 1 patient who had been diagnosed as having postviral chronic fatigue syndrome. Psychological contributors were next most common, followed by miscellaneous causes that included asthma or its treatment, environmental allergy, and neck torsion injuries.

Table 5 lists the treatments given to members of each group. Almost all were treated for reflux with either general lifestyle measures or medication. This is not surprising, since our ILS hypothesis supposes that even the "normal" amount of reflux stimulation will perpetuate laryngeal hyperirritability. As a matter of fact, we have come to feel that reversal of the central neural changes associated with ILS requires maximal acid suppression and we therefore use proton pump inhibitors regularly (omeprazole 20 mg twice a day, lansoprazole 30 mg daily, or, pantoprazole 40 mg daily).

TABLE 3. *ILS Symptom Triggers*

	L	L/O	D	D/O	O	Total
Total patients	5	20	4	6	4	39
Perfume	0	7	1	1	1	10
Other airborne	2	11	2	3	2	20
Reflux	3	16	3	3	3	28
Foods	3	7	0	0	2	12
Emotion	2	9	2	5	1	19
Voice use	1	6	2	0	1	10
Coughing	0	5	0	1	0	6
Exertion	0	1	1	0	0	2

TABLE 4. *ILS Possible Etiologic Factors*

	L	L/O	D	D/O	O	Total
Total patients	5	20	4	6	4	39
Reflux	5	18	3	4	3	33
Virus	2	10	3	1	1	17
Psychogenic	2	5	2	5	2	16
Asthma	1	5	1	1	1	9
Torsion injury	1	1	0	1	0	3
Enviromental allergy	0	4	0	1	1	6
Immune disorder	0	1	0	0	1	2

TABLE 5. *ILS Treatments*

	L	L/O	D	D/O	O	Total
Total patients	5	20	4	6	4	39
Reflux protocol	5	17	4	3	4	33
Reflux meds	4	19	3	3	3	31
Exercises	3	11	3	5	1	23
Psychotherapy	0	4	1	3	1	9
Botox	0	5	0	1	1	7
Massage/manipulation	0	4	1	3	0	8
Other	1	4	0	2	1	8

"Exercises" listed in the table include voice therapy with an emphasis on relaxation of laryngeal and associated muscular systems. Since the "sniff" maximally stimulates vocal fold abduction, many of the patients with laryngospasm will be asked to sniff repeatedly throughout the day.

Formal psychotherapy was a part of the treatment plan for only 9 of the 39 patients, but many received indirect psychological support and counseling from various members of the clinical team. Many of the patients came following a series of unsuccessful treatments, and simple reassurance that their disorder was understood may have been therapeutic.

Laryngeal manipulation or massage was effective in some patients, more so in those with dysphonia than laryngospasm. The technique used was a combination of those described by Aronson,[20] Harris and Lieberman,[21] and Roy et al,[22–23] with an emphasis on achieving release of tension in the thyrohyoid muscle region. If the first manipulation proved helpful, then it was generally repeated two or three times within a week or two. Botulinum toxin injections seem to be less effective, or not indicated, in patients with ILS as compared with those with focal laryngeal dystonia. Five of our 25 patients with laryngospasm received botulinum toxin injection at some point in their treatment, but 2 of these ultimately went on to require tracheotomy.

HYPOTHESIS FOR THE ETIOLOGY OF THE IRRITABLE LARYNX SYNDROME

We feel that the ILS develops in individuals as a reaction to some sort of central nervous system (CNS) change that leaves sensorimotor pathways in a hyperexcitable state. Clinical review makes it evident that there are a number of possible causative factors, and that several can be active in any one person. Emotional distress, habitual postural muscle misuse, GER, and postviral illness seem to be the most prevalent. A number of possible neuropathological processes can be considered in an examination of why these factors lead to chronic laryngeal motor stimulation and heightened sensory irritability.

A process termed *neural plasticity* may alter central neuronal control of the larynx and related structures. This implies a change or adjustment in the way that a central neuron reacts to an incoming stimulus. While these changes are important for memory and learning, plasticity may not be in the best interests of the individual and, in our example, may change the way that laryngeal motor systems react to sensations or thoughts. There are several processes by which central neurons may undergo plastic adaptation. In response to nerve or tissue injury, afferent inputs are withdrawn from the central neuron, which then makes new connections by resprouting dendrites or reactivating "silent" synapses, so through this process an afferent stimulus that used to result in one response now may elicit a different one.

Another mechanism for change in central neuronal function is a response to repeated noxious stimulation. Constant release of neurotransmitters activates plasticity-related genes in central neurons, such as *fos*. The probable mechanism for this is shown in Figure 1. When the first neurotransmitter stimulus arrives at the CNS neuronal cell wall, it sends a mes-

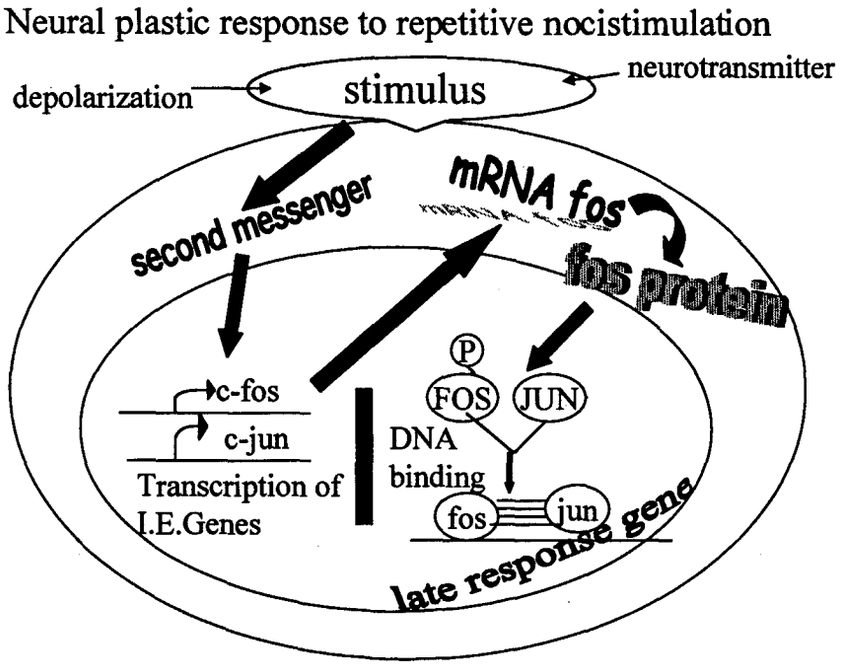

FIG. 1. Schematic representation of the process of neural plasticity. The center oval represents the CNS neuron nucleus, and the outer oval represents the cytoplasm. Repetitive noxious stimulation may eventually lead to permanent alteration of the cell genome.

sage through the cytoplasm by way of a second messenger to the nucleus, where immediate early genes such as *c-fos* or *c-jun* are induced. *C-fos* then moves out to the cytoplasm where *fos* protein is synthesized. The proto-oncogene *fos* then moves back into the nucleus, where it binds with DNA and regulates the transcription of late-response genes. The late-response genes may inhibit or stimulate neuronal activity and may alter the cell phenotype. If the cell phenotype is altered then the response to another afferent stimulus may be different than it was previously.

The body of literature on chronic pain is a helpful source of information and understanding about plasticity and its possible relation to development of ILS. In a review article on the contribution of central neural plasticity to pathological pain, Coderre et al[24] examined the evidence for ways that central neural plasticity can play a role in the development of pathological pain after peripheral tissue damage. Hyperalgesia depends, in part, on central sensitization, and while it is critical that initial inputs from the injury reach the CNS, the hyperalgesia does not depend on maintenance of inputs from the peripheral injury. Prolonged sensory disturbances associated with tissue injury are believed to result either from a reduction in the threshold of nociceptors, reduced inhibitory control, or increased excitability of CNS neurons involved in pain transmission. They further imply a contribution of C-fiber neuropeptides and excitatory amino acid (EAA) transmitters to noxious stimulus-induced changes in CNS function. These lead to an increase in the expression of proto-oncogenes such as *fos* and *jun*, which, as described above, participate in the regulation of mRNA encoding of dynorphin and enkephalin peptides, which can influence long-term changes in cellular function.[25]

Ludlow et al[26] have shown that disruption or injury of the sensory fibers coming from the larynx by way of the superior laryngeal nerve can result in hypersensitivity of the efferent motor supply to the thyroarytenoid muscles. Sensory afferents end in the nucleus of the tractus solitarius where second-order neurons relay a motor reflex to the nucleus ambiguus. Study subjects who had an earlier injury to the superior laryngeal sensory nerve supply, were found to have heightened motor reflex responses to electrical stimulation of the superior nerve on either the injured

or opposite side. In some cases the sensorimotor disinhibition led to the emergence of a focal dystonia-like spasmodic voice. It is felt that disinhibition may occur as a result of processes similar to that described above for pain.

The periaqueductal gray (PAG) area in the brainstem is involved in vocalization. Stimulation of the dorsal and lateral regions of the PAG evokes vocalization in some animals, and lesions produced here will result in mutism.[27,28] Cells in the caudal areas of the PAG have been found to have a relationship with laryngeal muscle activity. Supramaximal stimulation of the internal branch of the superior laryngeal nerve in the cat has been shown to increase *fos* labeling in dorsomedial and dorsolateral regions of the PAG.[29] This evidence suggests that neurons in this area are stimulated by laryngeal sensory fibers coming to the PAG, possibly via the nucleus of the tractus solitarius.

It is logical to assume that CNS viral infections, herpes zoster and others, can result in genome changes that alter laryngeal motor control.

Emotional connections affecting the larynx may work through the PAG, as it is well known that emotional states and defense reactions relate to PAG activity.[30,31] Jurgens[32] has proposed that the PAG serves as a link between sensory and motivation-controlling structures and the periambigual reticular formation, coordinating the activity of the different phonatory muscles. These studies support the obvious association between increased voice tension and psychological stress or repressed emotion.

Asthmalike reactions in parasympathetic parts of laryngeal muscle systems can be expected to respond to irritation in the same way as bronchial muscles in lower airway disease. The laryngeal effect may produce muscular tension voice problems, chronic cough, or laryngeal airway spasm rather than an "asthmalike" expiratory wheeze. As for reflux, we know that there is a direct reflex relationship between stimulation of the lower esophagus and thyroarytenoid muscle activity.[33] It also seems likely to us that chronic laryngeal reflux irritation affects the PAG, where neural plastic change results in long-term changes to laryngeal function.

Figure 2 graphically demonstrates how we feel the laryngeal CNS control network is affected by all the factors described—habitual, postural, psychological, reflux, and viral—to produce a hyperirritable "spasm-ready" state.

Figure 3 represents passage from the "spasm-ready" to ILS symptom manifest state. Muscular tone modulators may be present that make the spasm

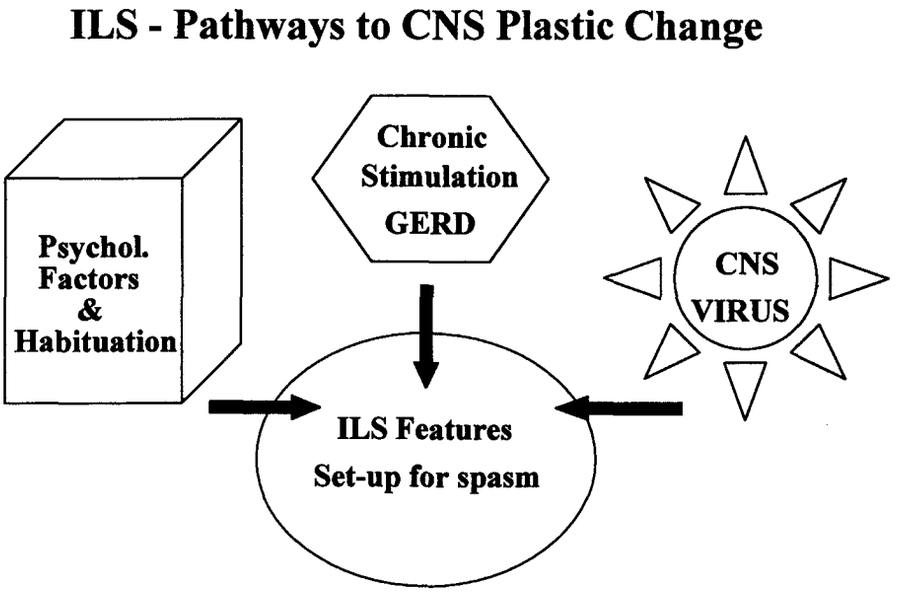

FIG. 2. Creation of a "spasm-ready" state in the CNS laryngeal control network. The oval region represents CNS neurons that may become hyperreactive in response to a number of processes.

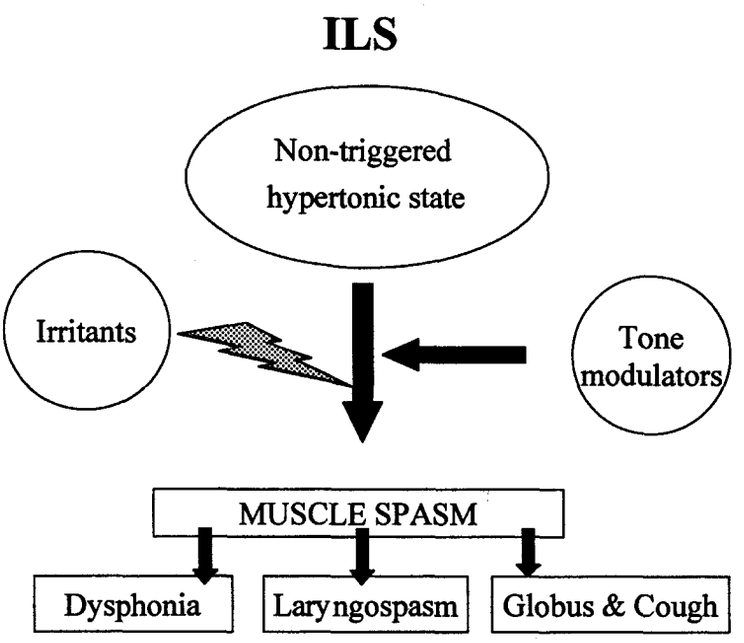

FIG. 3. The oval area represents the CNS laryngeal control networks in a hypertonic but non-triggered state. Other factors, such as general anxiety or poor posture, may increase laryngeal muscle tone globally, and are termed tone modulators. An irritant such as an airborne chemical or refluxate may trigger the muscle spasm.

more easily triggered by a sensory irritant. These tone modulators may include general psychological strain or postural factors. The trigger is usually a sensory irritant such as acid refluxate, airborne particles, or odors.

SUMMARY AND CONCLUSIONS

We believe that an "irritable larynx syndrome" exists in which hyperkinetic laryngeal dysfunction, as manifest by laryngospasm, dysphonia, globus, and/or chronic cough, is triggered by a sensory stimulus. We believe that ILS occurs when brainstem laryngeal controlling neuronal networks are held in a perpetual hyperexcitable state and therefore react inappropriately to sensory stimulation. We think that these changes result from an assorted collection of causes including habitual muscle misuse, emotional distress, viral illness, and chronic reflux stimulation.

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