IRRRITABLE LARYNX SYNDROME

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CW

- 48 y/o with 10 year history of episodic laryngospasm, choking and dysphonia. Symptoms occurred after blunt trauma in a boat in 1999.
- Multiple episodes per day of feeling like someone was putting hands around her throat and choking her.
- Multiple trips to the ER and unable to work
- Triggers include humidity, perfumes, touching her neck or turning her neck.

Mayo Clinic- “Vocal cord dysfunction”
- Started alprazolam for anxiety and weekly stress reduction sessions (Alexander technique)
- Referred here to see ENT and Speech
CW

- Treatment:
  - Physical therapy and speech therapy
  - Some improvement
- GI evaluation
  - Marked esophageal reflux and gastroesophageal noted.
  - PPI therapy, fundoplication, and domperidone
  - Some improvement
- Amitriptyline
  - Unable to tolerate but stopped because of side effects
- Tramadol
  - Helped a lot but too sedating
- Gabapentin
  - Dramatic improvement but still some symptoms

Irritable Larynx Syndrome

- Definition
- Etiology/Pathophysiology
- Symptoms
- Exam
- Diagnosis
- Treatment

Irritable Larynx Syndrome

- A chronic condition where laryngeal and pharyngeal muscles overreact to normal sensory stimuli
- Term first used by Morrison et al in 1999
- May cause:
  - Cough
  - Globus Sensation (lump in throat feeling)
  - Paradoxical Vocal Cord Motion
  - Laryngospasm
  - Dysphonia (Muscle Tension)
  - Neck and Throat Pain
  - Associated with Anxiety, Depression, and Headache

Irritable Larynx Syndrome

- Chronic = 6-8 weeks
- Usually Caused by Multiple Factors:
  1. External Stimuli
     - Smoking
     - Alcohol
     - Allergy
  2. Peripheral Neuropathy
  3. Central Sensitivity Syndrome

Irritable Larynx Syndrome

84% of ILS patients have one or more co-morbid disorders:

- 59% Irritable Bowel Syndrome
- 49% Headaches
- 43% Chronic Fatigue Syndrome
- 38% Fibromyalgia

Irritable Larynx Syndrome

- Chronic Cough is the most frequent presentation
- Can also present as:
  - Globus
  - Postnasal Drip
  - Inspiratory Stridor/Paradoxical vocal fold motion
  - Laryngospasm
  - Dysphonia

- Often presents as 2 or more of these symptoms
Chronic Cough

- Major quality of life issue
- Can be associated with:
  - Syncope
  - Urinary incontinence
  - Chest pain
  - Sleep disturbance
- 53% have clinical depression

Two Cough Pathways:

1. Central Pathway Voluntary
2. Peripheral Pathway Reflex

Reflex Pathway

- **Brainstem** (involuntary)
- "Laryngeal Adductor Reflex": Physical or chemical irritation is transmitted from the respiratory area to the brainstem which automatically sends a message back to the respiratory area to increase muscle tone (cough, throat clearing, laryngospasm, globus...)

  - An involuntary pathway that can be upregulated or downregulated by:
    1. The cerebral cortex
    2. Respiratory irritation
    3. Medications

Voluntary Pathway

- **Cerebral Cortex**
- Physical or chemical irritation is transmitted from the respiratory area to the brainstem which sends the information to the cerebral cortex, which becomes aware of the sensation of irritation

  - Cerebral cortex sends a message to the brainstem to initiate a cough response or try to suppress a cough response

  - Cerebral cortex control is related to the psychological characteristics (mood) of the patient

Cough (ILS) Pathway

- **Voluntary**
  1. Behavior modification
  2. Medication
- **Involuntary**
  1. Eliminate irritant
  2. Medication

Brainstem

Peripheral Nerve Stimulation
Reflex Cough vs Central Suppression

Cough Pathways:
1. Voluntary Pathway (Central)
2. Reflex Pathway (Peripheral)

Cough (ILS) Pathway

• Voluntary
  1. Behavior modification
  2. Medication
• Involuntary
  1. Eliminate irritant
  2. Medication

Genesis of Irritable Larynx Syndrome

External Stimulation (infection, trauma, reflux,...)
Laryngeal Adductor Reflex triggered
Abnormal modification of peripheral and/or central laryngeal sensory and motor response (maladaptation)
Abnormal muscle tension or spasm occurs in response to normal sensory stimulation

Laryngeal Irritability
Cough or muscle tension or spasm persists even after the initial external stimulation has been treated

Laryngeal Irritability
Three types of irritability:
1. Central Sensitivity Syndrome
2. Peripheral Sensory Neuropathy
3. Hypersensitivity of airway epithelium

Irritable Larynx Syndrome

Hypersensitivity of airway epithelium:
• “There is a fivefold increase in the number of nerve profiles that express TRPV1 in airway biopsies from subjects with chronic cough compared with normal controls.”
• TRPV1 is a pain receptor important in sensitivity to capsaicin, a potent stimulator of cough.
Laryngeal Irritability

“Laryngeal irritability has much in common with neuralgias and neuropathic pain syndromes.”

So medications used to treat chronic pain can help people with the Irritable Larynx Syndrome

Gibson et al, Expert Opinion Pharmacother. 2011, 12(11), p 1745-1755

Laryngeal Irritability as a Pain Syndrome

PAIN

• An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

CUGH

• An irresistible tickle in the throat in response to an external stimulation (virus, reflux, trauma...)

• A protective mechanism that helps clear excessive secretions and foreign matter from the airway

Why Pain?

Essential for protection from injury and recognition of the presence of injury

Pain

Nociceptive Pain

• Caused by stimulation of nociceptors (pain receptors) at the end of sensory nerves

• Different types of nociceptors:
  • Specificity of pain (nociceptor type) determined by which ion channel is expressed in the receptor

Neuropathic Pain

• Caused by damage to or dysfunction of the nerve itself

• Pain can be central or peripheral (or both)

• Suspect this when pain is out of proportion to the tissue injury

Nociceptive Pain Fibers

A-delta

• Thick fiber with thin myelin sheath

• Fast signal (5-30 m/s)

• Results in a sharp pain

C-fibers

• Thin fiber with thick myelin sheath

• Slower signal (0.5-2 m/s)

• Results in a dull or burning pain

Acute Injury:

• Results in a sharp pain first (A-delta) followed by a dull or burning pain (C-fiber)
Nociceptive Pain

- Common types of Nociceptors:
  - Thermal: Hot and Cold
  - Mechanical: Crush, Tear, Stretch
  - Chemical: Mustard, Cinnamon
- 28 known transient receptor potential nociceptors (TRP's)
- Laryngeal hypersensitivity seems to involve upregulation of the TRP nociceptors

Nociceptive Pain

28 Known TRP membrane receptors; 6 main subfamilies:
1. TRPC (canonical)
2. TRPV (vanilloid)
3. TRPM (melastatin)
4. TRPP (polycystin)
5. TRPML (mucolipin)
6. TRPA (ankyrin)

3 main receptors involved in cough:
1. TRPV-1 (Capsaicin and Resiniferatoxin - most potent proinflammatory known)
2. TRPM (Temperature)
3. TRPA (Mustard, Wasabi, Cinnamon)

Neuropathic Pain

Peripheral
- Nerve is injured by trauma (intubation, surgery, phonotrauma), infection (viral URI), or systemic disease (diabetes).
- Nerve has an abnormal regeneration, apparently with an abnormal increase in the number of Na channels.

Central
- Appears to involve an abnormal reorganization of the central somatosensory processing system.
- A “Central Sensitivity Syndrome”

Symptoms: Burning, Tingling, Sharp Shooting, Dull, Deep, Hyperesthesia

Treatment: Multimodal Therapy
1. Psychologic treatment - Anxiety, Depression
2. Physical therapy - Disuse atrophy, Maladaptive behavior
3. Medications

Neuropathic Pain

“Without concern for diagnosis, rehabilitation, and psychosocial issues, treatment (for neuropathic pain) has a limited chance of success.”
- Merck Manual Professional Version online, April 2014

Irritable Larynx Syndrome: Initial Irritants

1. Viral illness
   - Direct inflammation
2. Bacterial infection
3. Airborne irritants
   - Allergy
   - Environmental chemicals
   - Smoking
   - Asthma attacks
4. Gastroesophageal Reflux
5. Mechanical trauma
   - Intubation
   - Tracheal tubes cough, throat clearing, laryngeal irritation
6. Pulmonary problems
   - Asthma
   - Cancer
7. Foods
8. Psychological issues
   - Anxiety
   - Depression
   - Post-traumatic stress disorder
9. Medications
   - NSAIDs
10. Neuro
    - Neck surgery
    - Ulcers
    - Neurodegenerative disease
    - Aspiration
ACE Inhibitors (Lisinopril)

Bradykinin
- A peptide (a nine amino acid chain) naturally produced in the body
- Causes bronchoconstriction and vasodilation (lowers blood pressure)
- Plays a role in inflammation and pain

Angiotensin Converting Enzyme – ACE
- Enzyme that breaks down Bradykinin

ACE Inhibitor
- Medication that blocks ACE and prevents breakdown of Bradykinin
- Blocked ACE results in elevated levels of Bradykinin

TRPV1
- Pain receptor in the airway that is activated and sensitized by Bradykinin

Chronic Dry Cough
- Patients on ACE inhibitor have elevated Bradykinin which can cause a cough becuase of Bronchoconstriction, stimulation of TRPV1 pain receptors, and increased inflammation
- Can be associated with angioedemia when the patient is sensitive to and exposed to another environmental trigger

Irritable Larynx Syndrome

Symptoms
- Chronic cough
- Persistent minor dry cough
- Occasional or frequent episodes. Sometimes severe, violent cough paroxysms

Postnasal drip
- A chronic feeling of mucus in the throat

Chronic throat clearing
- Patient is often not aware of this

Paradoxical vocal cord motion
- "Exercise induced asthma"

Laryngospasm
- Severe episodic airway obstruction

Dysphonia
- Muscle tension

Triggers

3 Categories of Triggers
1. Caustic Irritation
   - Bleach, ammonia, dust, smoke, direct or aerosolized refluxate from the esophagus
2. Mechanical Irritation
   - Phonation, intubation
3. Emotional
   - Exposure to the subject of 9/11
   - Memories of 9/11
   - Anything that caused a heightened emotional state
   - All of these triggers caused a tonic, adductor closure of the glottis

Triggers (World Trade Center Experience)

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Treatment

Multidisciplinary, multipronged approach

3 level strategy:
1. Minimize Noxious Stimuli
   - Airborne irritants
2. Re-program the Habituated Laryngeal Response
   - Speech Therapy
   - Breathing Retraining
   - Behavior Therapy
3. Medications
Treatment

World Trade Center Experience:

• 80% of chronic cough patients respond to identification and treatment of a causative medical condition

• Of the 20% that do not resolve, 84% respond to speech therapy with medical therapy (antitussive drugs)

• 16% of chronic idiopathic cough patients do not respond to speech therapy and medical therapy
  • “Many of these patients have emotional triggers which is a much more difficult barrier to overcome”

McCabe et al. Am J Respir Crit Care Med 2012 186(5) p 402-403

1. Minimize Noxious Stimuli

Must Rule Out and Treat:

• Swallowing problems/aspiration
• Rhinosinusitis
• Pulmonary problems
  • Lung cancer, asthma, pneumonia
• Allergy
• Reflux
  • Esophageal (GERD) and laryngeal (LPR)
• Cardiac problems
• ACE inhibitors
• Neuro problems
  • Weakness, paralysis, tremor, sensory issues, spasmodic dysphonia
• Laryngeal lesions

1. Minimize Noxious Stimuli

Workup:

• Chest X-ray
• Allergy therapy and/or testing
• Reflux testing
  • pH probe and EGD
  • “Therapeutic trial” of reflux meds
• Nasal exam and CT sinuses if indicated
• Pulmonary evaluation
  • Refer for abnormal Chest X-ray
  • Pulmonary function studies (asthma, COPD, subglottic stenosis)
• Laryngeal exam
• Neurology evaluation if indicated
• Otolaryngology evaluation

GLOBUS

Airway Lesions

Dysphonia with cough 10 years
Cough with wheezing: Asthma?

Neurogenic

Globus after TIA
Cough after a virus
2. Re-program the Habituated Laryngeal Response

Evidence of Central Control of the Cough Reflex

1. Hutching et al showed that cough induced by inhalation of capsaicin can be voluntarily suppressed.
2. Placebo treatment for cough can cause a 50% reduction in cough frequency in patients with the common cold.
3. A randomized trial showed 87% of patients with idiopathic chronic cough improved with speech therapy compared to 14% of patients in a placebo group.

2. Vertigan et al. Lung 2012 190, p. 35-40

3. Medications

Antitussive Drugs:
- Can act centrally, peripherally, or both (nonspecific)

1. Opioids
   - Can help some but better for acute pain, less effective for chronic pain
2. Chronic Pain Medications
   - Antidepressants
   - Anticonvulsants
   - Statins
3. Topical Anesthesia
4. Dextromethorphan
5. TRP Receptor Antagonists
6. Botox
7. CBD?

Opioids

- Act by stimulating opioid receptors
- Can have a central or peripheral effect
- Opioid receptors found in:
  a. Cough centers in the brain
  b. Airway peripheral sensory nerves

Opioids:
1. Codeine
2. Hydrocodone
3. Morphine
4. Tramadol
5. BW443c
**Opioids**

Tramadol (Ultram)

- 2 actions:
  1. Binds to opioid receptors
  2. Inhibits reuptake of serotonin and norepinephrine
- Mild analgesic for acute and chronic pain
- Side effects:
  - Same as other opioids but less GI and less respiratory depression
  - Seizure risk at high dose or if pt is on an antidepressant
  - Less risk for dependence and abuse than other opioids

**Chronic Pain Medications**

- Used to treat long-term chronic neuropathic pain
- Off label use for cough
- Mostly central acting

**Chronic Pain Medications:**

1. Gabapentin
2. Pregabalin
3. Nortriptyline
4. Amitriptyline

- Seizure medicines also used to treat neuropathy
- Generally well tolerated but side effects at higher doses:
  - Drowsiness, dizziness, depression, peripheral edema, tremor
- Off-label use
  - Lee and Woo 2005: 68%-80% get symptom relief
  - Mintz and Lee 2006: 5/6 cases respond to Neurontin

**Chronic Pain Medication**

- Nortriptyline
- Amitriptyline

- Central acting tricyclic antidepressant that blocks the reuptake of serotonin and norepinephrine
- Approved for treatment of depression
- Off label use for headache, irritable bowel, chronic pain
- Side effects: Sedation, dry mouth, weight gain

**Chronic Pain Medications**

- Nortriptyline
- Amitriptyline

- Literature evidence:
  - Bastian 2006: 11/12 patients had "prompt" reduction in cough with amitriptyline
  - Jeyakumar 2006: 28 subjects randomized to amitriptyline or codeine for cough
    - Most of the amitriptyline subjects had complete response, none of the codeine subjects got complete response
  - Ryan and Cohen 2006: Amitriptyline 10mg/day up to 100mg/day
    - 67% had at least 50% improvement in symptoms
Chronic Pain Medications

Baclofen

- Central nervous system depressant
- Acts at the central nervous system and at spinal level by activating the GABA-b receptors (GABA is the chief inhibitory neurotransmitter)
- Used as a muscle relaxant and antispasmodic
- Low abuse potential but can have withdrawal symptoms

Dextromethorphan

- A non-narcotic codeine analog
- Central acting
- Over-the-counter and the most widely used antitussive
- Has only a small effect.

Grattan 1995

- Compared a 30mg dose to control in exposure to citric acid
- Cough reduction of 98% compared to control

Lee 2006

- Compared a 30mg dose to control in an acute viral URI
- Essentially no effect seen

Topical Analgesia

- Benzonate (Tessalon Perles)
- Lidocaine

- Acts as a local anesthetic to decrease sensitivity to stretch receptors and anesthetize the mucosa of the esophagus and airway
- Can cause increased risk for aspiration

TRP Receptor Antagonists

- Blocks peripheral pain receptors
- In research or clinical trials

TRPV1: acid (pH), temperature, capsaicin
- BCTC
- Resiniferatoxin
- Capsazepine
- Dihydropyrazine
- Vezuex

TRPA: pungent ingredients (mustard, wasabi, cinnamon, chemicals)
- AD-18
- HC-030031
- GRC 17536

TRPM: Hot and cold (especially cold)
- In research stage

Cannabidiol (CBD)

- One of at least 60 cannabinoids in the cannabis plant
- Minimally psychoactive (THC is the main psychoactive compound)
- Two primary cannabinoid receptors: CB1 and CB2

CB1: Primarily in the brain but also in peripheral tissue
- Maintain homeostasis by inhibiting excessive neuronal excitation and activity

CB2: Primarily in the immune system
- Helps modulate the immune inflammatory system
- Has been shown to improve neuropathic pain but not as good for nociceptive pain

Respiratory Retraining

Role of Speech Therapy

- Avoid triggers
  - Education to recognize, monitor and avoid triggers
- Functional control of the laryngeal adductor reflex
  - Increase awareness of laryngeal tension
  - Purposeful abduction of the cords with nasal sniff and pharyngeal relaxation
  - Identify and prevent throat clearing
- Forestalling the cough response
  - Help the patient gain cortical control over the brainstem
- Progressive desensitization
  - When the cough is controlled, consider gradually reintroducing the triggers
  - “Reset” the threshold of response by gradually desensitizing the patient
Respiratory Retraining

PK

May 2016
- Start gabapentin 200 mg q hs and 100 mg q am
- Speech therapy
- pH probe on no PPI positive for LPR; increase PPI to bid and GI referral

August 2016
- Dramatic response to gabapentin with in 3-4 days of starting
- GI evaluation + gastroparesis
- Symptoms resolve with speech therapy and aggressive reflux control so gabapentin stopped with no difficulties

PK


Bibliography

JG

• 72 y/o with cough for 1 year after heart surgery in January 2015
• Dry nonproductive cough with severe spasms frequently
• Triggers are talking and swallowing

April 2016 hospital consult:
• Good response to tramadol 50 mg tid and Amytryptiline 25 mg hs
• Voice clinic follow up after discharge

JG Clinic Visit

• Speech therapy at outside facility (MWB)
  • Near resolution of symptoms

• Wean meds
  • Tramadol 50 mg q am
  • Amitriptyline 25 mg q hs

KP

• 54 y/o with cough and laryngospasms x 4 years
• Seemed to start after getting a dog
• Cough episodes for several minutes 2-3 times per hour
• Severe traumatic laryngospasms several times per year
• Triggers: Cold air, talking, odors
• PPI therapy not helpful; Flonase helps some
• Symptoms completely resolved for 1 week while on vacation to Mexico

KP

• Tramadol 50 mg po tid x 7 days
• Refer to speech therapy
• pH probe on no PPI: Normal, so reflux meds stopped
• Refer for allergy evaluation

• 4 week results: Complete resolution of symptoms
VC

• 56 y/o customer service rep with 3 month history of cough
• Triggers: Yawning and talking
• Cough all day and wakes her up at night
• 3-4 episodes of laryngospasm per day
• Heartburn controlled with OTC Prilosec
• Presents with acute episode of dysphonia after a severe cough episode.

VC June 2015

VC July 2015

VC

Therapy:
• Voice rest for 1 week followed by speech therapy
• Gabapentin 200 mg hs and 100 mg am
• Increase PPI to bid
• Review ant reflux diet

MR
February 2015

EW
Cough with Ulcer
July 2016
RM

Rx: Voice Rest x 2 weeks followed by speech therapy along with Gabapentin 300 mg tid

Cough with Ulcer
August 2016
RM