Diagnostic criteria for cervical dystonia: Can botulinum neurotoxin manage, as well as, cure the problem?

Jill L. Ostrem, MD
Professor of Neurology
UCSF Department of Neurology
Movement Disorder and Neuromodulation Center
Bachmann Strauss Dystonia and Parkinson’s Disease Center of Excellence

December 6, 2015
Disclosures

Educational grant support:

Medtronic Inc., Merz, Inc., Boston Scientific, Allergan

Clinical trial support:

St. Jude Medical Inc., Boston Scientific
Objectives

• Review the diagnostic criteria for cervical dystonia
• Understand the role of oral medications in CD
• Discuss the use of botulinum neurotoxin injection in CD
• Outline the methods and procedures for determining the appropriate muscles for injection
• Understand the possible adverse effects of neurotoxin injections and the limitations
Dystonia

- A neurologic syndrome dominated by involuntary muscle contractions that may be sustained, patterned, or repetitive, frequently causing abnormal postures (twisting, flexion or extension, abduction or adduction)

- Classification:

  *Age of Onset: early (<21) or late (>21)*

  *Distribution or body region affected:*

    focal, segmental, multifocal, generalized

  *Etiology: idiopathic / primary (sporadic or inherited) or symptomatic / secondary*

- Multiple genes and risk factors known, but still account for relatively few cases
Dystonia is a brain circuit disorder

https://www.google.com/images/drprafullkdavemd.com
Cervical Dystonia

- Focal dystonia that produces patterned, repetitive, and spasmodic or sustained muscle contractions resulting in abnormal movements and postures of the head and neck

- *Cervical Dystonia* is preferred to the term spasmodic torticollis as an overarching descriptor, since Cervical Dystonia may or may not be spasmodic and may or may not consist of torticollis (head turning)

- In most cases, the exact cause is unknown
- Familial history of dystonia in approximately 12% of cases
- Previous neck trauma is common
- More common in women, mean onset 41 years
Dystonia Classification - New

- Age of onset (from infancy to late adult onset)
- Body distribution (focal forms, segmental, generalized)
- Temporal pattern (static or progressive disease course)
- Isolated or combined with another movement disorder (parkinsonism, myoclonus, or other neurological manifestations)
- Isolated dystonia
  - Onset in children = progress to generalized
  - Onset adulthood = remains focal or segmental
- Cause
  - Inherited (DYT, others)
  - Acquired (brain injury, tardive syndromes)
Cervical Dystonia

- Cervical Dystonia frequently begins as a pulling or drawing sensation in the neck or an involuntary twisting or jerking of the neck
- After onset, symptoms typically worsen, although the time course is highly variable (range: 1 month to 18 years)
- Progression typically plateaus within 5 years of onset
- Spontaneous remissions can occur but is rare
- No single test exists at this time to confirm diagnosis
- Neurologic examination is otherwise usually normal
- Sensory tricks—partial, temporary relief
Cervical Dystonia: Characteristics

- Subtypes (Torticollis, Laterocollis, Retrocollis, Anterocollis)
- Most patient present with a combination of these movements
- Each subtype activates different pattern of muscles resulting in the abnormal neck/head posture.
- Can also be associated with tremor


Cervical Dystonia: Treatment Options

- Oral medications have been used off-label
  - Trihexyphenidyl (Artane)
  - Clonazapam (Klonopin)
  - Baclofen
  - Other

- Surgery
  - Selective denervation
  - Deep brain stimulation

- Botulinum toxin therapy

Muscles involved in cervical dystonia

Torticollis
- Contralateral sternocleidomastoid
- Contralateral trapezius
- Ipsilateral splenius capitis
- Ipsilateral splenius cervicis
- Ipsilateral levator scapulae

Laterocollis
- Sternocleidomastoid
- Ipsilateral splenius capitis
- Ipsilateral scalene complex
- Ipsilateral semispinalis capitis and longissimus
- Ipsilateral levator scapulae
- Trapezius
Muscles involved in cervical dystonia

**Retrocollis**
- Bilateral splenius capitis
- Bilateral levator scapulae
- Posterior vertebral muscles (semispinalis capitis and longissimus)
- Upper trapezius

**Anterocollis**
- Bilateral sternocleidomastoid
- Scalene complex
Neck and Shoulder Muscles Affected in Cervical Dystonia

- Splenius capitis, 60-100 U
- Levator scapulae, 25-60 U
- Trapezius, 35-100 U
- Sternocleidomastoid, 40-70 U
- Scapulae complex, 15-55 U
Neck and Shoulder Muscles Affected in Cervical Dystonia

- **Splenius capitis**: 60-100 U
- **Longissimus**: 60-100 U
- **Splenius cervicis**: 60-100 U
- **Levator scapulae**: 25-60 U

- **Sternocleidomastoid**: 40-70 U
- **Trapezius**: 35-100 U
Botulinum Toxin

- Toxin temporarily weakens dystonic muscles, allowing for a more normal posture and function.
- Benefits depend on location and degree of dystonia of muscles being injected.
- Can not treat widespread or extremely severe generalized dystonia, as the toxin dose required would be too high.
- Toxin may be used to target specific dystonic muscles to improving aspects of care and function or relieve discomfort.
Botulinum Toxin Therapy

• Potent neurotoxin produced by bacterium *clostridium botulinum*

• 7 different serotypes – lettered A-G

• All serotypes are large proteins that act on cholinergic neuromuscular junctions to block transmission of synaptic vesicles.
Normal Neurotransmitter Exocytosis

A Normal Neurotransmitter Release

SNARE Proteins Form Complex

Vesicle and Terminal Membranes Fuse

Neurotransmitter Released

Acetylcholine

Acetylcholine Receptor

Muscle Fiber Contracts

Reproduced with permission from Arnon SS, et al. JAMA. 2001; 285:1061
Neurotransmitter Exocytosis: Intracellular Inhibition with BoNT

Botulinum Toxin Endocytosed

Light Chain Cleaves Specific SNARE Proteins

Types B, D, F, G

Types A, C, E

Type C

SNARE Complex Does Not Form

Membranes Do Not Fuse

Neurotransmitter Not Released

Botulinum Toxins

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>onabotulinumtoxinA</td>
<td>Botox®</td>
<td>Allergan</td>
</tr>
<tr>
<td>A</td>
<td>abobotulinumtoxinA</td>
<td>Dysport™</td>
<td>Ipsen</td>
</tr>
<tr>
<td>A</td>
<td>incobotulinumtoxinA</td>
<td>XEOMIN®</td>
<td>Merz</td>
</tr>
<tr>
<td>B</td>
<td>rimabotulinumtoxinB</td>
<td>Myobloc®</td>
<td>US WorldMeds/Solstice</td>
</tr>
</tbody>
</table>

- Neurotoxin Products contains highly purified botulinum toxin protein refined from the bacterium *Clostridium botulinum*
- Some have A and Some have B Serotypes
- All toxins has a heavy chain and a light chain bound by a di-sulfide bound
Units of neurotoxins and dosing are not interchangeable

The potency Units of BOTOX® (onabotulinumtoxinA) for injection are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, Units of biological activity of BOTOX® cannot be compared to nor converted into Units of any other botulinum toxin products assessed with any other specific assay method.²
Cervical Dystonia Neurotoxin Injection Results

- 70% of patients get >60-80% benefit
- Patients with long-duration dystonia respond less well than those treated earlier
- Side effects occur in 10% of patients (most common, transient difficulties with swallowing)
- Pain is also often improved
Injection of Botulinum Toxin Technique

- A small needle is placed into the target muscle
- In large or accessible muscles, confirmation of appropriate placement may be achieved by feeling the muscle
- In small or deep muscle groups, EMG may be required
- Well tolerated
- Local anesthetic cream or sedation can be used
What to Expect From BOTOX® Therapy

- Many patients begin to notice an effect within 4 weeks of treatment

- It's Important to Set Realistic Treatment Goals:
  - Patients have clear view of treatment expectation
  - Other members of the treatment team can become involved in helping the patient meet that goal
  - Common treatment goals may include:
    - Use good hand to open fingers enough to clean affected hand
    - Be better able to move loved one's elbow when helping to dress them
    - Need less force during physical examination

Duration of Botulinum Toxin Effects

- The effects of treatment with BTX are usually greatest for a 2-6 week period following injection.

- These effects usually fade after about 3 to 6 months.

- Re-injection of the toxin is usually performed every 3 months.
ADVERSE REACTIONS

• Blepharospasm:
  – eyelid ptosis (19%)
  – dry mouth (16%)
  – visual impairment (12%)
  – diarrhea (8%)
  – headache (7%).

• Cervical Dystonia:
  – dysphagia (13% -18%)
  – neck pain (7% -15%)
  – muscle weakness (7% -11%)
  – musculoskeletal pain (4% -7%)

• Limb dystonia:
  – weakness

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.
Caution for Use

- BTX should be used with extreme caution in patients:
  - myasthenia gravis
  - amyotrophic lateral sclerosis (ALS)
  - Taking anticoagulants
  - Taking certain antibiotics - aminoglycosides
**Immunogenicity**

- Botulinum neurotoxin is a protein that serves as an antigen.
- The development of an antibody response is dependent on:
  - *Larger doses of botulinum toxin*
  - *Larger cumulative doses*
  - *Injections administered at less than 3 months intervals*
  - *Controversial if newer Xeomin may have less immunogenicity*
- Formation of neutralizing antibodies results in resistance to beneficial effects.
- Antibodies to BTX may be detected using various methodologies.
- Clinicians often use in vivo tests: frontalis test.
- If resistance occurs, replacing one serotype with another may be effective.
Final thoughts

- Neurotoxin injections are first line therapy for CD.
- They can alleviate symptoms, but not cure the disease.
- Injections need to be maintained every three months.
- Can allow for greater easy and effectiveness of PT.
- Can co-exist with cervical spine degenerative issues.
UCSF and SFVA Movement Disorders Team

Movement Disorder and Neuromodulation Center
Jill L. Ostrem, MD, Medical Director
Philip Starr, MD, PhD, Surgical Director

Neurology
Jill Ostrem, MD
Nicholas Galifianakis, MD
Caroline Tanner, MD, PhD
Marta San Luciano, MD
Maya Katz, MD
William J. Marks, Jr., MD
Robert White, MD, PhD
James Maas, MD, PHD
Chadwick Christine, MD
Michael Aminoff, MD
Robert Edwards, MD
Ken Nakamura, MD, PhD
Alexandra Nelson, MD, PhD
Michael Geschwind, MD

Research Support Staff
Sarah Wang, PhD
Kristen Dodenhoff, BA
Michael Dodge, BA
Janet Allen, BA
Shatara Blackmon
Yasmeen Gonzalez
Jeverly Calaunan
Kathleen Comyns, MPH
Samantha Konz, BS
Samantha Betheil, BA
Cheryl Meng, MPH

Psychiatry
Andrea Seritan, MD

Neurosurgery
Philip Starr, MD, PhD
Paul S. Larson, MD
Edward F. Chang, MD
Daniel Lim, MD, PhD
Krzysztof Bankiewicz, MD, PhD
Coralie De Hemptonne, PhD
Nicki Swann, PhD
Andrew Miller, BA
Witney Chen PhD
Doris Wang, MD, PhD

Neuropsychology
Caroline Racine Belkoura, PhD

Nursing
Monica Volz, FNP, MS
Robin Taylor, FNP, MS
Lorna Beccaria, RN
Karen Merchant, MSN
Susan Heath, MS, RN
Rigzin Lama, LVN

Fellows
Erica Byrd, MD
Jennifer Chen, MD
Cameron Dietiker, MD
Nijee Luthra, MD, PhD
Svjetlana Miocinovic, MD, PhD
Brian Lee, MD

Social Work
Monica Eisenhardt, LCSW

Physical Therapy
Nancy Byl, PT, PhD
Heather Bhide, PT