Treating Cervical Dystonia

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Disclosures

Ib R. Odderson MD, PhD has reported that he has nothing to disclose.
Goals and Objectives

- To describe clinical aspects relevant to the diagnosis of cervical dystonia
- To provide the clinician with available options for treatment in patients with cervical dystonia
- To allow clinicians to determine the process of determining candidates for treatment of chemodenervation
- To provide clinicians with an introduction to techniques of botulinum toxin injections for cervical dystonia
Recognizing Dystonia

- A motor disorder characterized by inappropriate muscle contraction
  - Sustained ("tonic") contractions usually result in abnormal postures
  - Irregular, unsustained ("clonic") contractions often result in jerky movements
    - may occur frequently enough to resemble tremor
  - Both contraction types occur in consistent patterns characteristic of each individual
  - Both are often present simultaneously
Recognizing Dystonia

- Multichannel electrophysiological characteristics
  - Co-contraction:
    - simultaneous activation of antagonistic muscles
  - Overflow:
    - recruitment of muscles not normally involved in specific actions
  - Electrophysiological analysis not used in routine clinical practice

- No definitive diagnostic laboratory tests
  - Other than DNA analysis of genetic forms
Recognizing Cervical Dystonia

- Cervical dystonia (CD)
  - a.k.a. spasmodic torticollis
  - A focal form of dystonia involving the neck
    • the most common area of the body affected by dystonia
  - Featuring head postures and movements produced by dystonic cervical muscles
  - Direction(s) of movement determined by specific muscles involved
Recognizing Cervical Dystonia

- Head movement may involve any combination of 3 directional planes, plus horizontal shifts:
  - Flexion/extension ("pitch")
  - Right/left rotation ("yaw")
  - Right/left tilt ("roll")
  - Horizontal shifts
    - anterior/posterior (A-P)
    - lateral right/left
Head Postures in CD

Torticollis 82%–97%
Laterocollis 42%–63%
Retrocollis 29%–32%
Anterocollis 14%–25%

Most patients exhibit a combination of these postures
Head Postures in CD

Laterocollis: *ipsilateral*
- M. levator scapulae (M)
- M. semispinalis cervicis (M)
- M. scalenus medius (S)
- M. longissimus cervicis (S)

Torticollis: *ipsilateral*
- M. semispinalis cervicis (M)
- M. levator scapulae (M)
- M. splenius cervicis (S)
- M. longissimus cervicis (S)

Anterocollis: *bilateral*
- M. scalenus medius (M)
- M. levator scapulae (M)
- M. longus colli (S)

Retrocollis: *bilateral*
- M. semispinalis cervicis (M)

Lateral shift: Combination of laterocollis to one side and laterocaput to the opposite site

Correspondent muscles

Laterocaput: *ipsilateral*
- M. sternocleidomastoideus (M)
- M. trapezius pars descendens (M)
- M. sternocleidomastoideus (M)
- M. splenius capitis (M)
- M. semispinalis capitis (S)
- M. longissimus capitis (S)
- M. levator scapulae (S)

Torticaput: *contralateral*
- M. trapezius pars descendens (M)
- M. sternocleidomastoideus (M)
- M. semispinalis capitis (S)
- M. longissimus capitis (S)
- M. obliquus capitis inferior (M)
- M. levator scapulae (M)
- M. splenius capitis (S)

Anterocaput: *ipsilateral*
- M. longus capitis (M)
- M. levator scapulae (M)
- M. semispinalis capitis (S)
- M. trapezius pars descendens (M)

Retrocaput: *bilateral*
- M. obliquus capitis inferior (M)
- M. semispinalis capitis (M)
- M. trapezius pars descendens (M)

Anterior shift: Combination of anterocollis and retrocaput

Correspondent muscles
Recognizing Cervical Dystonia

- Head movement may involve any combination of 3 directional planes, plus horizontal shifts
  - Flexion/extension ("pitch")
  - Right/left rotation ("yaw")
  - Right/left tilt ("roll")
  - Horizontal shifts
    - Anterior/posterior (A-P)
    - Lateral right/left
Head Postures in CD

- **TORTICOLLIS**
- **LATEROCOLLIS**
- **FLEXION/EXTENSION**

- **LATERAL SHIFT**
- **SAGITTAL SHIFT**
Cervical Dystonia - Clinical Features

- “Sensory tricks”
  - Physical maneuvers or gestures that ameliorate dystonia
    - in a way that cannot be explained by simple opposition to the dystonic movement
  - Approximately 75% of cervical dystonia patients report sensory tricks
  - Although called “sensory”, the mechanism by which they work is unknown

Cervical Dystonia - Clinical Features

- **Pain**
  - CD and limb dystonia are the only focal dystonias that commonly cause pain
  - About 2/3 of CD patients experience significant pain
  - For many CD patients, pain is their most bothersome symptom
Examination for Cervical Dystonia

- Observe spontaneous head movements during history-taking

- Ask the patient not to oppose the dystonia
  - Observe head and shoulder posture
    - Rotation/tilt/lateral shift from front view
    - Flexion/extension/anteroposterior shift from side view
  - Observe symmetry of muscle mass

- Examine range of neck motion in 3 planes
  - Observe any directional limitation
  - Observe any rotation or tilt on neck extension

- Examine postures and movements while walking
  - Observe shoulder posture from posterior view

- Examine for dystonia in other body regions
Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)

- Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)
  - 85-point maximum standard rating scale for severity of CD used in clinical studies

- Multiple scores assigned for 3 different aspects of CD
  1. Objective head movements/postures
  2. Subjective disability
  3. Pain

- Time-consuming; not often used in routine clinical practice
Differential Diagnosis of CD

Consists of disorders that cause:

- Neck pain
  - Numerous musculoskeletal causes
  - Cervical arthritis often coexists with CD

- Abnormal head postures/movements
  - Also may have musculoskeletal origins
  - The most common movement disorder mimicking CD is essential tremor (ET)
    - 50% of ET patients have head tremor
### Differential Diagnosis – Essential Tremor

<table>
<thead>
<tr>
<th>Cervical dystonia</th>
<th>Essential tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Tonic and/or irregular clonic movement</td>
<td>– Regular, rhythmic oscillation</td>
</tr>
<tr>
<td>– Directional head posture</td>
<td>– Neutral head position</td>
</tr>
<tr>
<td>– Usually directional range of motion restriction</td>
<td>– No restriction of range of motion</td>
</tr>
<tr>
<td>– Pain often prominent</td>
<td>– No pain</td>
</tr>
<tr>
<td>– Upper limb tremor absent or not prominent</td>
<td>– Prominent postural and kinetic upper limb tremor</td>
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Cervical Dystonia – Delayed Diagnosis

- Despite the fact that:
  - CD appears to be a distinctive syndrome
  - CD is the most common form of dystonia

- Many patients encounter a delay in diagnosis
  - in recently diagnosed (2001-2012) CD cases:
    - mean time to diagnosis was 14.8 months
    - after seeing a mean of 3.0 providers

- Timely identification of cervical dystonia requires clinical knowledge and vigilance
Epidemiology & Disease Course

- Mean age of onset ~ 42 years
- Women : men = 2:1
- Typical disease course
  1. Insidious onset
  2. Progression over 5-10 years
  3. Stabilization
Etiology

- **Heredity**
  - ~ 10% of CD patients have a positive family history
  - 3 known genetic forms: DYT23, DYT24, DYT25
  - other genetic forms of dystonia may present with CD

- **Identifiable non-hereditary causes include:**
  - Acute dystonia secondary to anti-dopaminergic drugs
  - Tardive dystonia
  - Trauma
  - Congenital

- **But most cases are sporadic and idiopathic**
Management

- Education regarding limits of knowledge
  - Unknown: what causes CD or how to cure it
  - Unknown: what is wrong in the CNS or how to fix it

- Symptomatic nature of treatment
  - Treatment is aimed at reducing abnormal muscle contractions
  - Non-curative, need for ongoing therapy

- Discuss realistic goals of treatment
  - Establish patient priorities re symptoms
  - Discuss success rates and risks associated with each treatment modality
Potential Goals of CD Treatment

- Normalization of head posture
  - Reduce reliance on sensory tricks
- Reduction of clonic movements
- Relief of pain
  - Successful pain relief may produce patient satisfaction, regardless of effects on head posture
- Reduction of disability
  - Record scope and severity prior to initiation of treatment
CD Treatment Options

- Oral medications
- Botulinum toxin injections
- Surgery
- Other
### Oral Medications for CD

**Drugs reported to be useful in CD:**
- **Anticholinergic drugs**
  - trihexyphenidyl, diphenhydramine, benztropine, others
- **Benzodiazepines**
  - clonazepam, others
- **Baclofen**
- **Levodopa, dopamine agonists**
- **Tetrabenazine (presynaptic dopamine depletor)**
- **Dopamine antagonists**
- **Others**

**All drugs are designed and approved for other indications**
- None are FDA-approved for dystonia
- Utility in dystonia discovered by trial and error, or happenstance

The sheer variety underlines our lack of understanding of the pathophysiology of CD

Antagonistic drugs suggest different pathophysiology in different individuals
Oral Medications for CD

- No oral medication provides adequate monotherapy for a majority of individuals with CD
  - Oral drug therapy consists of sequential trials of medications, hoping to find one that benefits

- Benefit is usually only partial, with significant residual symptoms and disability

- Side effects are common

- Bottom line: Few patients are content with oral medication therapy alone
  - But patients often find them useful as adjuncts
Botulinum Toxin for CD

- Botulinum toxin (BT) is the treatment of choice for CD
  - Efficacy and safety established in multiple DBPC trials
- More effective than any other option
- Fewer side effects than oral medications
- Much less risky than brain surgery

Limitations:
- More costly than most oral medications
- Benefits wear off after several months; thus repeated injections are necessary for ongoing symptom control
Botulinum Toxin for CD

- Four available BT preparations
  - Botox® (onabotulinumtoxin A)
  - Dysport® (abobotulinumtoxin A)
  - Myobloc® (rimabotulinumtoxin B)
  - Xeomin® (incobotulinumtoxin A)
    - CD is the only indication for which all 4 toxins have been FDA-approved

- No accepted dose equivalence or conversion ratio between different toxin preparations

- Few head-to-head studies
  - Clinical experience suggests they are equally effective for CD
Botulinum Toxin for CD

- BT works by preventing acetylcholine release at the neuromuscular junction
  - A process known as “chemodenervation”

- BT action depends on incorporation into motor neuron terminals in target muscles

- Thus successful treatment with BT depends on:
  1. Proper identification of muscles involved in CD
  2. Selecting an appropriate dose of toxin
  3. Delivering the toxin where it can reach the neuromuscular junction
Identification of Muscles Involved in CD

Based on:

- **Patient reporting of:**
  - Direction of involuntary movement/pulling sensation
  - Spontaneous pain

- **Observation of:**
  - Head/shoulder posture and spontaneous movement
  - Muscle mass
  - Range of motion

- **Palpation for hypertrophy, clonic contractions, and tenderness**

- **Knowledge of:**
  - Cervical muscle anatomy
  - Mechanical action of major muscles contributing to head deviation(s)
Muscles Most Often Injected for CD

- CD PROBE: observational study of 1,041 CD patients undergoing BT therapy
  

- Muscles most often injected:
  - Splenius capitis (86.1%)
  - Sternocleidomastoid (76.9%)
  - Levator scapulae (67.3%)
  - Trapezius (63.6%)
  - all others under 33%
Selecting an Appropriate Dose of BT

- Must be tailored to the individual patient based on:
  - Severity of head and neck deviation
  - Localization of pain
  - Muscle bulk
  - Age
  - Response to prior injections

- Initial dosing in a naive patient should begin conservatively
Selecting an Appropriate Dose of BT

Manufacturers' recommended dose ranges for cervical dystonia:

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Botox®</th>
<th>Dysport®</th>
<th>Myobloc®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levator scapulae</td>
<td>20-100 U</td>
<td>50-200 U</td>
<td>1,000-2,500 U</td>
</tr>
<tr>
<td>Splenius capitis</td>
<td>15-100 U</td>
<td>75-450 U</td>
<td>1,000-2,500 U</td>
</tr>
<tr>
<td>Sternocleidomastoid</td>
<td>15-100 U</td>
<td>50-350 U</td>
<td>1,000-2,500 U</td>
</tr>
<tr>
<td>Trapezius</td>
<td>20-100 U</td>
<td>50-300 U</td>
<td>1,000-2,500 U</td>
</tr>
<tr>
<td>Scalene complex</td>
<td>15-50 U</td>
<td>50-300 U</td>
<td>500-1,000 U</td>
</tr>
<tr>
<td>Semispinalis capitis</td>
<td>30-100 U</td>
<td>50-250 U</td>
<td>1,000-2,500 U</td>
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</table>

The manufacturers of Xeomin® state only "The recommended initial total dose of XEOMIN for cervical dystonia is 120 Units" without individual muscle recommendations.
Delivering the Toxin

- Motor nerve terminals are mainly located near the midpoint between the origin and insertion.

- Thus toxin delivery should be concentrated around the central region of the muscle.

- In many CD patients, specific musculature can be identified by surface inspection or by palpation.
Cervical Muscles – Surface Anatomy

- Splenius capitis
- Trapezius
- Levator scapulae
- Sternocleidomastoid
Delivering the Toxin

- In other patients, particularly with considerable adipose tissue or for less frequently injected muscles, muscle detection may require assistance
  - Electromyography
    - Detects muscular tissue and active contraction
    - Does not distinguish between muscles
  - Ultrasound
    - Allows visual confirmation of muscle injection
    - Especially useful to distinguish layered muscles
- Both techniques require thorough knowledge of neck muscle anatomy
Botulinum Toxin for CD

- A key aspect of BT treatment is an informed patient
- Discussions should include:
  - Time course of benefit
    - Onset mean (7 days) and range (1-14 days)
    - Time to maximum benefit (up to 3 weeks)
    - Duration of benefit (ideally 3 months or more)
  - Specific expected benefits
    - Allows patients to make/report pertinent observations about type, magnitude and duration of effects
  - Potential side effects
  - Costs and insurance coverage
Botulinum Toxin for CD

Additional topics for discussion with patients:

- “Trial and error” approach to BT therapy
  - Determining the appropriate muscles and doses may require multiple sets of injections to fine-tune
  - First injections based on what is known generally about BT
  - Subsequent injections guided by the individual’s prior responses

- Options available to improve results include:
  - Increasing doses, changing muscles to increase benefit
  - Decreasing doses, changing muscles to minimize side effects
  - Adding muscle localization technology (EMG, ultrasound)
  - Changing toxins
Side Effects of Botulinum Toxin for CD

- Excess weakness of targeted muscles
  - Patients may report head heaviness, or difficulty raising head when bending or lying down

- Diffusion of toxin leading to weakness in non-targeted muscles
  - Dysphagia is common with injection of anterior cervical muscles

- Atrophy, similar to anatomic denervation
  - Most visible in sternocleidomastoid

- Development of immune resistance
  - Occurs after repeated injections
  - Associated with short interinjection intervals, high doses
Surgical Options for CD

- Surgery is the riskiest and costliest option
- Reserved for CD patients who fail to respond adequately to BT or oral medications
- Success rates fall between those for BT and those for oral medications
- Two procedures:
  - Deep brain stimulation (DBS)
  - Selective denervation (SD)
Deep brain stimulation (DBS)
- Pulsatile electrical stimulation of bilateral globus pallidus internus via implanted electrodes
Surgical Options for CD

- Prospective study
  - 10 patients refractory to BT followed for ≥ 5 years
  - Mean total TWSTRS improvement: 54.5 ± 27.4%
    • but only 3/9 had > 50% improvement in pain scores
  - Blinded video mean improvement: 47.6 ± 15.4%
  - 2 patients required lead replacement for infection:
    • Improvement mostly sustained by unilateral stimulation for 3 and 2 years respectively
  - 3 patients developed micrographia, 2 dysarthria

Surgical Options for CD

- **Selective denervation (SD)**
  - Surgical destruction of peripheral innervation of muscles deemed to be involved in CD

- **Prospective study**
  - 68% of 37 patients who failed BT obtained meaningful benefit from SD
  - Mean magnitude of benefit was 20-40% on the three TWSTRS subscores
  - 37.5% developed dysphagia, mostly transient
  - Reinnervation was detected within 6-12 months in 45% of sternocleidomastoids and 20% of splenii

Focused Ultrasound for Essential Tremor

- Focused Ultrasound
  - Non-incisional approach
- FDA approved for treatment of Essential Tremor
- High energy US transducer helmet
Other Treatments for CD

- Physical therapy (PT)
  - Stretching exercises may improve range of motion
  - But PT has a limited role in dystonia
  - Essentially, dystonic muscles already get too much exercise; what they need is something to relax them
Other Treatments for CD

- Anecdotal reports of benefit for:
  - Acupuncture
  - Massage
  - Mindfulness/meditation
  - Hypnosis
  - Yoga
  - Numerous disciplines described online

- But formal clinical studies are lacking
Conclusions

- Cervical dystonia is a clinical diagnosis
  - Awareness by physicians leads to prompt diagnosis

- Management is symptomatic
  - Engaged interaction with patients is key to success

- Botulinum toxin injections are the treatment of choice
  - Proper application requires knowledge of anatomy, toxin dosages, and technical proficiency

- Other treatments are potentially useful