Understanding Cervical Dystonia and treatment with botulinum toxin

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Disclosures

• Research: Dystonia Coalition; National Institutes of Health
• Compensation/honoraria for services as a consultant or an advisory committee member: Acadia, Acorda, Adamas, AEON pharmaceutical, Allergan, Inc; Jazz pharmaceutical; Impax Pharmaceuticals; Ipsen Biopharmaceuticals, Inc; Revance.; Merz Pharmaceuticals; US World Meds; Sunovion, Teva Neurosciences
• Royalties: Cambridge, Humana Press; Wolters Kluwer
Cervical dystonia
Multiethnic population

- Complex focal dystonia
- Most frequent focal dystonia in clinical practice
- Prevalence: approximately 50 per million
- Minimum incidence: 1.18 per 100,000 person-years
- Peak age of onset 4th-5th decade
- Female: male ratio: 3-4 : 1

- Family history in up to 25%
  - genes identified: THAP1, CIZ1, ANO3, GNAL

Defazio et al. Tremor Other Hyperkinet Mov 2013
LaHue et al Move Disord 2020
Cervical dystonia

• Diagnosis based on clinical features
  – Mean interval between symptom onset and diagnosis of 24-44 months
  – Mean number of providers before diagnosis: 3.8
  – 50% patients with harmful effects from delay

• Possible reasons
  – Lack of awareness of CD
  – No validated diagnostic criteria
  – Lack of confirmatory diagnostic testing

Tiderington et al, J Neurol Sci 2013
LaHue et al Move Disord 2020
Proposed diagnostic criteria
Cervical dystonia

- Patterned, repetitive head/neck movement/postures
- Spontaneous or triggered by motor tasks
- Head tremor may be present
- Presence of effective sensory trick
- Dystonia in other body parts

DeFazio et al. Neurological Sciences 2019
Likely not CD

- Fixed involuntary head posture
- Weakness of neck muscles
- Ability to mentally suppress the movements or postures
- Diplopia induced by voluntary correction of abnormal posture

DeFazio et al. Neurological Sciences 2019
Cervical dystonia: Phenomenology
Overlying spasms
Tremor and CD

• 20% - 60% with tremor
  – 80% in neck alone
  – 20% combined with hand tremor
• Onset tremor corresponds to onset CD
• Presence of tremor increased risk of spread to other body regions
• May identify a clinical subtype of CD

Defazio et al, JNNP 2013
Avanzino et al. Neurology 2020
Geste Antagoniste
(Alleviating Maneuver, Sensory trick)

- Photographic Illustration of the Seven Cases
  Presented by Brissaud in his 1894 Lesson.

Broussolle et al. Tremor and Hyperkin Disorders 2015
Geste Antagoniste
(Alleviating Maneuver, Sensory trick)

• 40-80% with geste
• Can be a touch, visual input, postural
• Touching chin, back of head most frequent
• Postural changes may also have impact

Schramm et al. Move Disord 2004
Kaji et al. Move Disord 2013
Filip et al. J Neural Transm 2016
Cervical Dystonia: “Natural History”

- Largely unknown; Dystonia Coalition study in progress
- 20% temporary remissions
- < 1% permanent remissions
- > 5 years, often stable
- Neck posture may change
- 11% with spread, 90% to contiguous body area, usually to arm

Weiss et al, Mov Disord 2006
Non-motor features

- Pain 68-75%
- Disability
  - Loss or reduced employment
  - Inability to drive
  - Social embarrassment
- Psychiatric complications
  - Depression (30-50%)
  - Anxiety disorders (30-50%)
Pathophysiology of dystonia

- A “network” disorder with abnormal output likely basal ganglia, cerebellum and cortex

- Defect in sensory function and sensorimotor integration
  - Spatial and temporal domains

- Maladaptive plasticity
  - Somatosensory cortex with larger receptive fields and overlapping representation (digits in hand dystonia)

- Loss of surround inhibition
  - Overactive direct pathway, underactive indirect pathway

Jinnah HA, Hess E. Parkinsonism Rel Disord 2018
Treatment of CD

• Botulinum toxin: treatment of choice

• Oral medications
  – None approved for use in CD
    • levodopa, anticholinergics, baclofen, clonazepam, tetrabenazine
  – Adverse effects frequent

• DBS
FDA approvals of BoNT for CD

• Serotype A
  – OnabotulinumtoxinA (Botox®)
  – IncobotulinumtoxinA (Xeomin®)
  – abobotulinumtoxinA (Dysport®)

• Serotype B
  – RimabotulinumtoxinB (Myobloc®, Neurobloc®)

• Most common adverse effects: dysphagia, dry mouth, neck weakness

Simpson, Neurology 2008
Comella J Neurol 2011
Spiegel et al. Toxins 2020
Botulinum Neurotoxins

Chen et al. Toxins 2012, 1196-1222
BoNT Mechanism of Action

Montal M. Ann Rev Biochem 2010
Newer concepts of BoNT mechanism

• May not be solely a peripheral effect

• Central effects important (muscle afferents)
  – Normalization of altered brain network activity
  – Normalization of left/right asymmetries of white matter microstructure (fractional anisotropy)

Brodoehl et al. Neuroimage Clin 2019
Blood A et al. Frontiers Neurology 2019
Recovery of NMJ following BoNT

Approximately 10-12 weeks of benefit but “yo-yo” effect

Comella et al. J Neurol 2020
Patient satisfaction with BoNT A Prospective Study

Colosimo et al. J Neurol 2019
DaxibotulinumtoxinA for cervical dystonia
Results of open label tolerability study

- Side effects:
  - Dysphagia 14% all mild
  - Muscle weakness 5% (1 mild, 1 moderate)
  - Neck pain 3%

Jankovic et al. Move Disord Clin Prac 2018
Results of pivotal trial (Apen study)
Oct 14, 2020

• 301 CD subjects
• Randomized 1:3:3 (placebo, 125U Daxi, 250U Daxi)
• 11-13 point improvement in TWSTRS
• Median duration: 20-24 weeks
• Side effects
  – Dysphagia 1.6-3.9%
  – Muscle weakness 2.3-4.7%
BoNT serotype E

- Faster onset of action (within 1 day)
- Faster waning of effect (2-4 weeks)
- In development: Allergan, Ipsen

Davies et al. Toxins 2018
Pons L et al. Toxins 2019 abstract

* Data provided by Bonti, recently acquired by Allergan
Based on BOTOX ® Cosmetic Label – Efficacy not collected prior to day 7 (Not based on head to head studies with EB-001)
**EB001-GL201 Study Cohort 7
Technique
Analysis of head position
<table>
<thead>
<tr>
<th>Posture</th>
<th>Ipsilateral</th>
<th>Contralateral</th>
</tr>
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<tbody>
<tr>
<td>Horizontal turn</td>
<td>Splenius</td>
<td>SCM</td>
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<td></td>
<td>Longissimus</td>
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<td>Longissimus</td>
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<td>Levator scapulae</td>
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<tr>
<td>Anterocollis</td>
<td><strong>SCM</strong></td>
<td><strong>SCM</strong></td>
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<td></td>
<td>Scalene</td>
<td>Scalene</td>
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<td></td>
<td>Longus colli</td>
<td>Longus colli</td>
</tr>
<tr>
<td>Retrocollis</td>
<td><strong>SPL</strong></td>
<td><strong>SPL</strong></td>
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<tr>
<td></td>
<td>Longissimus</td>
<td>Longissimus</td>
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<tr>
<td></td>
<td>Upper trapezius</td>
<td>Upper trapezius</td>
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<tr>
<td></td>
<td>Semispinalis</td>
<td>Semispinalis</td>
</tr>
<tr>
<td></td>
<td>captitis</td>
<td>captitis</td>
</tr>
<tr>
<td>Shoulder elevation</td>
<td>Levator scapulae</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trapezius</td>
<td></td>
</tr>
</tbody>
</table>
Colli: C3-C7; Caput: head and C1

Reichel G. Basal Ganglia 2011
Tatu L, Jost WH. J Neural Transm 2016
Jost WH. Tremor and other Hyperkinetic Movements 2019
Targeting injection into appropriate muscle

• Determination of possible muscles involved
  – Clinical examination (caput, colli)
  – Palpation and inspection (hypertrophy, pain)

• Targeting dystonic muscles for injection
  – Electromyography
  – Electrical stimulation
  – Ultrasound
  – Imaging
Targeting muscles

- Omohyoides
- Ant. jugular vein
- Sternohyoides
- Sternothyreoides
- Trachea
- Esophagus
- 6th cervical vertebra
- Vertebral vessels
- Scaleneus anterior
- Scaleneus medius
- Splenus colli
- Levator scapula
- Semispinalis colli
- Semispinalis capitis
- Splenus capitis
- Trapezius
- Thyroid gland
- Common carotid artery
- Int. jugular vein
- Vagus nerve
- Ext. jugular vein
EMG assisted selection and injection
Increased magnitude of improvement with EMG guidance

- Randomized, double-blind study comparing BoNT injections administered with and without EMG guidance
- No difference in dose administered
- Equal number of patients improved in both groups
- Those in EMG guided group:
  - Greater magnitude of improvement
  - Larger number of patients with marked improvement

» Comella et al. Neurology 1992
Ultrasound injections

- Direct visualization
- Deep muscles
- Avoid structures
- Improved outcomes

- Expensive
- Requires specific training

Farrell et al. Toxins 2020
Long-term treatment with OnabotulinumtoxinA in cervical dystonia

- 326 CD patients enrolled
  - 251 completed
  - 75 discontinued
    - Lost to follow up
    - Adverse events
- 86% ≥ 5 treatments
- Duration 128 weeks
- Onabot dose: 187 MU
- All negative MPA at baseline
  - 1.2% with + MPA during the course
    - All continued to respond
  - 73 patients with one failed injection despite negative MPA, follow-up responsiveness

Brin et al. Move Disord 2008
BoNT in a real world setting

- Approximately 30-40% of CD patients discontinue BoNT
  - Lack of efficacy
    - Dose/muscle selection; complex CD
  - Adverse effects
  - Unrealistic expectations
  - Expense
  - Inconvenience

Jankovic J Neurol Sci. 2015
Comella and Bhatia. J Neurol 2015
Brashear et al. Mov Disord 2000
Jinnah et al J Neurol 2016
Lack of benefit: Causes

- Wrong muscles injected
  - Lack of knowledge of functional anatomy
  - Change in dystonic posture
- Suboptimal dose
- Muscles inaccessible to injection
- Antibody mediated resistance
CD and BoNT Conclusions

- CD is a focal dystonia that is complex and heterogeneous
- BoNT regarded as treatment of choice
- Up to 40% discontinue therapy
- New treatments needed
  - Pharmacologic
  - New formulations of BoNT
  - Effective approaches using DBS
Thank you

It has been an honor to participate in the first AOS virtual MDS Botulinum Toxin Conference 2020