New Treatment Considerations for Movement Disorders

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Botulinum Toxin

- 1817: Food-borne botulism 1st reported by Christian Kerner
  - Kerner later proposed toxin’s therapeutic use for movement disorders
- 1981: Alan Scott reported use of toxin for strabismus
- Widely used for disorders of abnormal, excessive or inappropriate muscle contractions

Mechanism

- Blocks neurotransmitter release at peripheral cholinergic nerve terminals
  3 steps
- Binding to receptors on unmyelinated presynaptic membrane
- Neuronal uptake by endocytosis & translocation
- Inhibition of transmitter exocytosis from presynaptic terminal

Management of Spasticity

- Oral Baclofen
- Selective Dorsal Rhizotomy
- Botulinum Toxin
- Surgery

GENERAL
- Reversible
- Focal
- Permanent
Seven immunologically distinct toxins
- Type A most used and studied
- Type B newest released
- Animals immunized with one serotype did not neutralize another serotype
- Some evidence suggesting cross-reactivity

Available Preparations
- Type A
  - BOTOX®
  - Dysport®
- Type B
  - Myobloc™
  - NeuroBloc®

FDA Approved Uses
Botox®
- Blepharospasm
- Strabismus
- Hemifacial spasm
- Cervical Dystonia
- Severe primary axillary hyperhidrosis
FDA Approval
BOTOX® COSMETIC

Indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator (brings brows together) and/or procerus muscle (lowers brows) activity in adult patients ≤ 65 years of age.

FDA Approval
Myobloc™

- Cervical Dystonia

Other Uses

- Headache
- Palmer Hyperhidrosis
- Sialorrhea
- TMJ associated muscle spasms
- Myoclonus
- Limb dystonia
- Laryngeal dystonia
- Tics
- Spasticity

Botulinum Toxin Properties

- Onset of clinical effect is 24 - 72 hours
- Clinical effects are typically seen within 1 week of injection
- Peak effect 4 - 6 weeks
- Average duration of effect is sustained 3 - 4 months
**Botulinum Toxin**

**Advantages**
- Rare systemic side effects
- Adverse effects usually transient
- Dose can be varied to parallel disease course

**Side Effects**
- Injection site pain
- Excessive weakness
- Dry Mouth, constipation, urinary retention, respiratory depression/apnea
- Dysphagia – typically local reaction
- 2 – 5% of patients receiving repeated injections develop blocking antibodies

**Botulinum Toxin Disadvantages**
- Short acting
  - Patient compliance
  - Repeated injections
- Local acting
  - Large muscle groups may require several injection sites
- Increased joint range of motion may decrease overall stability

**Iatrogenic Botulism**
- Case report of 3-y/o girl w/ diplegia due to PVL
  - 40 U/kg botulinum toxin type A
  - Dysphagia w/ in 10 days followed by excessive drooling and aspiration in 3 – 4 weeks
  - Apneic spells during sleep
  - Generalized weakness 1 month post injection lasting 6 weeks
Iatrogenic Botulism: Take 2

  - Case report of 10-y/o boy spastic quad. previously injected with botulinum toxins A and B
    - 812 U/kg botulinum toxin type B
    - Apneic episodes during sleep and noisy breathing 1 week after injections
    - Progressive dysphagia, facial diplegia, neck weakness
    - Bronchoscopy revealed hypotonic palate
    - Back to baseline w/in 6 months after injections

Safety

- Chart review of 108 patients receiving high-dose botulinum toxin A
  - ≥ 15 U/kg or ≥ 800 units
  - Total 209 injections; 15 - 30 U/kg (< 45 kg)
  - Median 2/pt at median interval 5 months
  - Dx: CP 78%, TBI 15%
  - 1 SAE in kids < 45 kg - mild botulism
    - Received 23 U/kg

Type A in Children < 2 years

- 74 cases
  - Most common OBPP 72% (1y/o), CP 25% (74%
    2y/o)
  - Avg dose 6.5 U/kg (1y/o) & 8.4 U/kg (2y/o)
  - Max dose 14.3 U/kg
  - Only AE reported focal or generalized weakness
    * ~4% in 1-y/o and 6.5% in 2-y/o
    * Lasted 1 - 4 days

Type B: Pilot Study

- Open-labeled, 29 pts., ages 3 - 19 years
- Most spastic quadiparesis
- SEs 24%: xerostomia most frequent
- Max dose recommended 400 U/kg or ≤10,000 units

Goldstein M. *J Child Neurology*, 2006

Pascual-Pascual, S.I. *European Journal Paed Neuro*, 2008

Schwerin A. *Pediatric Neurology*, 2004
Evidence-based Review

- Report of the Therapeutics and Technology Assessment Subcommittee of the AAN -- Neurology, Feb 5, 2009
- 6 Class 1 articles
  - Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population.
- Recommendations:
  - Injections of the calf should be offered as a treatment option for equinus varus deformity
  - Considered for treatment of adductor spasticity and pain control in children undergoing adductor-lengthening surgery
  - Considered as a treatment for UE spasticity

Dystonia

- Definition: neurologic movement disorder characterized by sustained muscle contractions, usually producing twisting and repetitive movements or abnormal postures or positions
- Primary dystonia
  - Dystonia the only sign
  - History & labs unrevealing
    - DYT1 mutation in many childhood onset cases
    - Other inherited or sporadic forms
- Secondary dystonia
  - Associated neurologic disorders

Neurologic Syndromes Causing Secondary Dystonia

- Dopa-responsive dystonia
- Parkinsonism
- Wilson’s disease
- Gangliosidoses
- Metachromatic leukodystrophy
- Lesch-Nyhan syndrome
- Homocystinuria
- Hartnup disease
- Glutaric acidemia
- Leigh’s disease
- Mitochondrial encephalomyopathies
- Familial basal ganglia calcifications
- Cereoid-lipofuscinosis
- Ataxia-telangiectasia
- Neuroacanthocytosis
- Huntington’s disease
- Pantothenate Kinase-associated neurodegeneration

Classification of Dystonia

- Focal: single body region
- Segmental: two or more contiguous body regions
- Multifocal: noncontiguous body regions
- Generalized
- Hemidystonia: unilateral
Dystonia Treatment

- **L-dopa**
  - Recommended that any child with unexplained dystonia
  - Response is often dramatic if the child has DRD
  - May also be helpful in some children with dystonia due to cerebral palsy, or perhaps in other metabolic disorders or structural abnormalities
- **Trihexyphenidyl (Artane®)**
  - Most commonly used medication for children
- **Others**
  - Diazepam, clonazepam, valproate, baclofen, carbamazepine, reserpine, or tetrabenazine (FDA approved for HD Aug 2008)
  - Botulinum toxin
  - Intrathecal baclofen

Deep Brain Stimulator

DBS Background

- **1970s - 1980s**
  - Thalamus main target from PD patients
- **1990s**
  - Trend in favor of pallidum
    - Renaissance of posteroverentral pallidotomy in PD
    - However, pallidotomies associated with reduction in clinical improvement over time
- **DBS**
  - 1977: Thalamic DBS for dystonia with good results
  - 1980s: Ventral intermediate nucleus of thalamus
    - Mild to moderate limb improvement, not axial
  - 2001: GPi in PD
Dystonia associated with prefrontal overactivation

Activa Dystonia Therapy
- Indicated for unilateral or bilateral stimulation of the GPi or the STN to aid in the management of chronic, intractable (drug refractory) primary dystonia in patients seven years of age and above, including:
  - Generalized dystonia
  - Segmental dystonia
  - Hemidystonia
  - Cervical dystonia (torticollis)

Activa Dystonia Therapy: Patient Selection
- Patients experiencing progressive disability or pain.
- Failed reasonable medication treatments including Artane, Baclofen and a benzodiazepine alone or in combination.
- Negative trial of Levodopa to rule out possibility of dopa-responsive dystonia (DRD).
- Failed treatment of focal dystonia with botulinum toxin injections.
- Patient’s in whom the expected benefit will outlast the inherent risks of the surgical procedure.

Outcome
- Most patients to date have DYT1 mutations
- Trial in secondary dystonias
  - Improvement in patients with pantothenate kinase-associated neurodegeneration
- Risks
  - Intracranial hemorrhage or infection
  - Hardware failure
  - Some reports of dysexecutive syndrome and other cognitive effects
  - Important to get stimulator in posteroventral portion of GPi
  - Stimulation of anterodorsal border of GPi can cause significant worsening