Cerebral palsy: the emerging role of deep brain stimulation

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Goals of Tone Management

• Improve function
  – Mobility
  – Communication
  – Independence
• Pain reduction
• Reduce secondary complications
  – Deformities
  – Skin breakdown
• Caretaker burden

Tone characterization

<table>
<thead>
<tr>
<th>Tone</th>
<th>Movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Hypokinetic</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>Hyperkinetic</td>
</tr>
<tr>
<td>Hypertonia</td>
<td></td>
</tr>
<tr>
<td>– Spasticity</td>
<td>– Athetosis</td>
</tr>
<tr>
<td>– Dystonia</td>
<td>– Chorea</td>
</tr>
<tr>
<td></td>
<td>– Ataxia</td>
</tr>
<tr>
<td></td>
<td>– Mixed</td>
</tr>
</tbody>
</table>
Hypertonia

<table>
<thead>
<tr>
<th>Spasticity</th>
<th>Dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Velocity dependent resistance</td>
<td>• Non velocity dependent</td>
</tr>
<tr>
<td>• Uniplanar</td>
<td>• Multiplanar</td>
</tr>
<tr>
<td>• Hyper-reflexia</td>
<td>• Reflexes variable</td>
</tr>
<tr>
<td>• Ashworth</td>
<td>• Burke-Fahn-Marsden</td>
</tr>
<tr>
<td>• Tardieu</td>
<td>• Barry Albright</td>
</tr>
</tbody>
</table>

Hypertonia Management Options

- Physiotherapy
- Orthotics
- Medications
- Neurotoxins (botulinum, phenol, alcohol)
- Neurosurgical options
- Orthopedic options (tendons, bones)

Hypertonia Assessment Tool

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hypertonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased involuntary movements/postures with tactile stimulus to another body part</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Increased involuntary movements or postures with movement if a distal body part</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Velocity dependent resistance to stretch</td>
<td>Spasticity</td>
</tr>
<tr>
<td>Presence of a spastic catch</td>
<td>Spasticity</td>
</tr>
<tr>
<td>Equal resistance to passive stretch during bi-directional movement of a joint</td>
<td>Rigidity</td>
</tr>
<tr>
<td>Increased tone with movement of a distal body part</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Maintenance of limb position after passive movement</td>
<td>Rigidity</td>
</tr>
</tbody>
</table>
**Spasticity**

- Hypertonia in which “resistance to externally movement increases with increasing speed of stretch and varies with the direction of joint movement and/or in which resistance to externally imposed movement rises rapidly above a threshold speed or joint angle.”

  Sanger et al; Pediatrics 2003; 111:e89-97

**Treatments for spasticity**

- Therapy
- Oral pharmacocology
  - Baclofen, tizanidine, benzodiazepines
- Targeted therapies
  - Botulinum toxins
- Neurosurgical
  - Selective Dorsal Rhizotomy
  - IntraThecal Baclofen

**Dystonia**

Repellent muscle contractions that result in uncontrolled twisting or writhing movements

Functionally may include co-contraction of agonist/antagonist muscle groups.

- Burke-Fahn Marsden
- Barry Albright
- UDRS
Dystonias

Primary
• Genetic
  – Progressive
  – Paroxysmal
  – Focal or generalized
• Structural
• Biochemical

Secondary
• Injury
  – Mechanical
  – Non-progressive
  – Progressive
• Metabolic
  – Progressive
  – Non-progressive

Primary Progressive, Secondary progressive, Secondary non-progressive

Burke-Fahn Marsden - Motor

<table>
<thead>
<tr>
<th>Region</th>
<th>Provoking Factor</th>
<th>Severity Factor</th>
<th>Weight Factor</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>0-4</td>
<td>0-4</td>
<td>0.5</td>
<td>0-8</td>
</tr>
<tr>
<td>Mouth</td>
<td>0-4</td>
<td>0-4</td>
<td>0.5</td>
<td>0-8</td>
</tr>
<tr>
<td>Speech/ Swallow</td>
<td>0-4</td>
<td>0-4</td>
<td>1.0</td>
<td>0-16</td>
</tr>
<tr>
<td>Neck</td>
<td>0-4</td>
<td>0-4</td>
<td>0.5</td>
<td>0-8</td>
</tr>
<tr>
<td>R. Arm</td>
<td>0-4</td>
<td>0-4</td>
<td>1.0</td>
<td>0-16</td>
</tr>
<tr>
<td>L. Arm</td>
<td>0-4</td>
<td>0-4</td>
<td>1.0</td>
<td>0-16</td>
</tr>
<tr>
<td>Trunk</td>
<td>0-4</td>
<td>0-4</td>
<td>1.0</td>
<td>0-16</td>
</tr>
<tr>
<td>R. Leg</td>
<td>0-4</td>
<td>0-4</td>
<td>1.0</td>
<td>0-16</td>
</tr>
<tr>
<td>L. Leg</td>
<td>0-4</td>
<td>0-4</td>
<td>1.0</td>
<td>0-16</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>N/120</td>
</tr>
</tbody>
</table>

Barry-Albright Dystonia Score

<table>
<thead>
<tr>
<th>REGION</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>0-4</td>
</tr>
<tr>
<td>Mouth</td>
<td>0-4</td>
</tr>
<tr>
<td>Neck</td>
<td>0-4</td>
</tr>
<tr>
<td>Trunk</td>
<td>0-4</td>
</tr>
<tr>
<td>Left Arm</td>
<td>0-4</td>
</tr>
<tr>
<td>Right Arm</td>
<td>0-4</td>
</tr>
<tr>
<td>Left Leg</td>
<td>0-4</td>
</tr>
<tr>
<td>Right Leg</td>
<td>0-4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>N/32</td>
</tr>
</tbody>
</table>
**BFM D Disability Rating Scale**

<table>
<thead>
<tr>
<th>Region</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Writing</td>
<td>0-4</td>
</tr>
<tr>
<td>Speech</td>
<td>0-4</td>
</tr>
<tr>
<td>Feeding</td>
<td>0-4</td>
</tr>
<tr>
<td>Eating</td>
<td>0-4</td>
</tr>
<tr>
<td>Hygiene</td>
<td>0-4</td>
</tr>
<tr>
<td>Dressing</td>
<td>0-4</td>
</tr>
<tr>
<td>Walking</td>
<td>0-6</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>N/30</td>
</tr>
</tbody>
</table>

**Pharmacologic options for dystonia**

- Acetylcholine antagonist
- α Adrenergic agonist
- Dopamine supplementation
- Dopamine agonist
- Dopamine antagonist
- Dopamine depletion
- Gaba-B agonist
- Gaba-A agonist
- Chemodenervation
- Trihexyphenidyl
- Clonidine, Tizanidine
- Levodopa/carbidopa
- Requip/Mirapex
- Risperidone
- Tetrabenazine
- Baclofen, Bz'd's
- Zolpidem
- Botulinum toxins A, B

**Neurosurgical options**

**spasticity**
- Rhizotomy
  - GMFCS I-II
- ITB
  - GMFCS I-V

**dystonia**
- DBS
- ITB
Deep Brain Stimulation: Mechanism

- Delivery of electrical impulses to the brain in order to modify neuronal circuitry

Proposed mechanisms:
- Inhibit local firing of Gpi and STN
- Single pulse
- Increases with train of pulses
- Inhibition duration increases with stimulation intensity
- Background interference – local effect
- Direct stimulation of circuits – downstream activation


Dystonia in CP

- The Basal Ganglia

Opportunities for success: Primary Implants
n = 68 (9/2007 – 05/13)

Secondary dystonias
N = 51
- CP (29)
- NBIA (5)
- CVA (3)
- TBI (2)
- HIE (4)
- Other (8)
- GA1 (2); AT (1); DDON (1); PDH (1); TD (1); PKGD (1)

Primary dystonias
N = 17
- Dy6-1 (14)
- Other (3)
Program: Team

Patient Assessment

• Neurology – 3
• Neurosurgery – 1
• Genetics
• Clinical nurse specialist
• PT/OT
• Neuropsychology
• Bio-behavioral therapist
• Child life specialist
• Research coordinator
• Clinic coordinator
• Family liaison

Operating Room

• Neurosurgery
• Neurology
• Anesthesia
• Child life
• Radiology
• Technical support

DBS: Patient selection

• Age ≥ 7 years
• Dystonia
  – Diagnostic studies – imaging, biochemical, genetic
• Rating scales
• Oral medication trials
• Psychosocial assessment
• Psychological screening
• +/- ITB trial

CP: Patient Characteristics

Table I. Patient demographics and DBS lead information.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Fire</th>
<th>Size</th>
<th>DBS Lead</th>
<th>With Trogol</th>
<th>Lead/Tip Coordinates</th>
<th>Actual Setting</th>
<th>Voltage (V)</th>
<th>Face Width (mm)</th>
<th>Body Width (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>18</td>
<td>48, 50</td>
<td>00, 00, 00</td>
<td>X: 2,00, 1,40, 0,0</td>
<td>0,65</td>
<td>1500</td>
<td>250</td>
<td>300</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>10</td>
<td>55, 64</td>
<td>00, 00, 00</td>
<td>X: 3,00, 2,40, 0,0</td>
<td>0,35</td>
<td>1200</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

Note: This table provides patient demographics and DBS lead information. The lead/Tip coordinates are measured from the midpoint of the lead to the tip and are shown as [X, Y, Z] in millimeters. The actual setting refers to the intensity and location of the stimulation. The voltage (V) and face and body width (mm) are crucial for the effective treatment of movement disorders.

Marks, et al; Movement Disorders 2011;
Bilateral pallidal DBS for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study

- 13 adults; choreoathetoid-dystonic CP
- Mean BFMDRS improvement 21.1% at 1 year – 34.7 (baseline) – 24.4 (1 year)
- Stimulation rate 130
- Functional disability, pain, mental health related QOL all improved

Vidhaillet: Lancet Neurology 2010
MetaAnalysis: Outcome

<table>
<thead>
<tr>
<th>Measure</th>
<th>% improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMDRS-M; n=61</td>
<td>24.9% overall</td>
</tr>
<tr>
<td>- 6 months; n=39</td>
<td>24.1% (p=0.001)</td>
</tr>
<tr>
<td>- 6-12 months; n=31</td>
<td>25.96% (p=0.001)</td>
</tr>
<tr>
<td>- &gt;12 months; n=11</td>
<td>17.1% (p=0.001)</td>
</tr>
<tr>
<td>BFMDRS-D; n=53</td>
<td>10.01% (p&lt;0.001)</td>
</tr>
<tr>
<td>- 6 months; n=31</td>
<td>8.36% (p=0.001)</td>
</tr>
<tr>
<td>- 6-12 months; n=30</td>
<td>8.04% (p=0.044)</td>
</tr>
<tr>
<td>- &gt;12 months; n=7</td>
<td>12.03% (p=0.073)</td>
</tr>
</tbody>
</table>

Marks et al J Child Neurol 2013 in press

DYT-1 vs DCP

- All patients undergoing DBS (Sept 2007- Aug 2012)
- Primary implants
- Age 7-15 years at implant
- Diagnosis Dyt-1 dystonia or cerebral palsy (DCP)
- Followed for at least 12 months post implant
- Medtronic sponsored HDE protocol
- IRB approved database
- Independent study nurse reviews protocol
- Rating scales – therapists blinded to specific stimulation parameters
- BFMFRS-M.D; BAS
- ANOVA 2 way analysis

Dystonia Implants  n = 60 (9/2007 – 8/2012)

Primary dystonias N=14
- DYT-1 (11)
- Other (3)

Secondary dystonias N=46
- CP (28)
- NBIA (4)
- CVA (4)
- TBI (2)
- HIE (3)
- Other (8)
Dystonia Implants (n= 60)

Primary dystonias
• N = 14
  – Mean 12.41 +/- 5.6 years
  – Median 13 year
• Dyt-1 = 11
  – Mean 10.6 +/- 3.7 years
  – Median 9.5 years
• Non Dyt-1 = 3
  – Mean 13.3 +/- 3.9 years
  – Median 13 years

Secondary dystonias
• N = 46
  – Mean 14.5 +/- 5.3 years
  – Median 15 years
• CP = 28
  – Mean 14.8 +/- 5.3 years
  – Median 15 years
• Non=CP = 18
  – Mean 14 +/- 5.4 years
  – Median 13 years

Baseline

DCP (n=9)
• 11.02 +/- 3.09 years
• M:F 6:3
• BFM-M: 75.7 (120)
• BFM-D: 22.1 (30)
• BAS: 24.4 (32)
• 34.78 +/- 12.17 months
  – Range: 19-55 months
• 16.5 (+/- 4.04) mm lateral
• 75 Hz

Dyt-1 (n=8)
• 10.15 +/- 2.93 years
• M:F 3:5
• BFM-M: 36.2 \( p=0.004 \)
• BFM-D: 10.5 \( p=0.002 \)
• BAS: 12.3 \( p<0.001 \)
• 29.63 +/- 9.32 months
  – Range 20-40 months
• 15.66 (+/- 1.46) mm lateral
• 75 Hz

B&F Motor (120)
Summary

- Deep brain stimulation of the globus pallidus is effective at reducing motor dysfunction in patients with dystonia due to Dyt-1 and CP
- There is corresponding reduction in disability
- Patients with Dyt-1 have ongoing gradual improvement and may take months to stabilize
- CP patients seem to respond more quickly, but less completely
Conclusions

• Degree of motor improvement was higher in the CP group at 6 months (31% vs. -0.7%) and 12 months (24% vs. 6%), but not at 18 months. Overall motor impairment remains higher in the CP pts (p = .082)
  – Dyt-1 patients better at baseline and at follow-up to 1 year and beyond
  – CP patients improve faster, plateau earlier
  – Dyt-1pts – gradual but steady improvement
Conclusions

• Disability (BAS)
  – Both groups improved; no statistical differences between CP and Dyt-1 cohorts were noted in functional status 12 months. \( P = 0.003 \) This similarity was lost at 18 months.
  – Overall disability remained higher in the CP cohort at all points. (\( P = 0.009 \))

Discussion

• The 1 year motor improvement in out DCP patients is reflective of overall worldwide experience - Koy et al, 2012
• More work needs to be done
  – Long-term follow-up
  – Patient selection, target optimization, stimulation parameters
  – Regional body differences
  – Quality of life
  – Economic impact

MALUUF

Gimeno et al. 2013; Eur J Ped Neurol
Upper Extremity

GMFCS - ambulation

I: Walk and climb stairs; running with decreased speed, balance, or coordination.
II: Limited walking on uneven surfaces.
III: Walk with ambulation device; W/C for long distance.
IV: Power chair for long-distance.
V: Restricted voluntary motor control; limitations in all areas of motor function.

Children with CP of every severity level by GMFCS often have both spasticity and dystonia

Summary

- Effectiveness shown in improving motor rating scales
- Small gains in function can be important in improving quality of life
  - Reducing contracture load
  - Reducing caretaker burden
  - Hand and finger function
  - Pain
  - Not always reflected by current rating scales
- Quality of life and neuropsychological impacts needs to be formally addressed
- International registry