Treatment of children with hemiparesis -
basic science, botulinum toxin

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• Neuroplastic changes by Constraint Induced Movement Therapy
• Botulinum toxin therapy
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• Botulinum toxin therapy
Team

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• Introduction
  – Neuronal plasticity
  – Congenital hemiparesis
  – Aim of the study

• Methods

• Results

• Conclusions
Plasticity

Ability to modify and compensate for loss of structure / function

Ability to adapt to different tasks

Neuromodulation

Strategies to influence (motor) function and cortical plasticity
Prerequisite for normal development

Adaptation to different tasks
Haslinger, B., P. Erhard, et al. (2004). "Reduced recruitment of motor association areas during bimanual coordination in concert pianists." Hum Brain Mapp

Compensation after harm
e.g. congenital stroke
Inadaequate plasticity might interfere with function
Kaltenbach et al., Tinnitus as a plastic phenomenon and its possible neural underpinnings in the dorsal cochlear nucleus. 2005 Hear. Res
Quartarone et al, Task-specific hand dystonia: can too much plasticity be bad for you? Trends Neurosci. 2006
• Adult stroke patients

• 2 weeks of CIMT

• TMS: increase in excitability in M1

• fMRI: increase in BOLD effect in M1

Liepert et al 2001, J Neurol; 248: 315-21
Congenital Hemiparesis
MRI findings

12 weeks of gestation
30 weeks of gestation
40 weeks of gestation
Congenital hemiparesis
M1

Staudt et al 2002, Brain;125:2222-37
Congenital hemiparesis

To study adaptive neuronal plasticity in congenital hemiparesis
Study design
• 12 days

• 10 hours „Constraint“

• 2 hours 1 to 1 physiotherapy

• 8 hours group therapy
Exclusion

- AED
- Bilateral MRI pathology
- Bilateral corticospinal projections
- < 10 y
- Cerebral malformations
- Botulinum Toxin treatment (within last 6 months)

Inclusion

- MRI scan
- TMS examination
- Central motor conduction time within the normal range
- MACS level 2
- Defective lesion
- n = 7
- age = 12y (12-30)

- n = 9
- age = 13y (11-30)
Results - WMFT

**WMFT - quality**

- **pre**: Green box plot with mean and standard deviation, p-value labeled as p=0.016*
- **post**: Green box plot with mean and standard deviation, p-value labeled as p=0.007*
- **f.-up**: Light green box plot with mean and standard deviation

**WMFT - time**

- **pre**: Blue box plot with mean and standard deviation, p-value labeled as p=0.018*
- **post**: Blue box plot with mean and standard deviation, p-value labeled as p=0.051*
- **f.-up**: Light blue box plot with mean and standard deviation, p-value labeled as p=0.008**
Results - TMS

- Pre: p=0.018
- Post: p=0.043
- F-up: p=0.612

Comparison between pre, post, and f-up conditions with significant differences at pre and post, but not at f-up.
- 1.5 T Scanner Siemens Avanto
- Block design
- Active / passive palmar flexion / extension
- Online pressure and frequency recording
- SNPM 3: changes in BOLD effect
Summary

• improvement of motor function

• Neuroplasticity:
  - increase of excitability of M1
  - increase of BOLD effect

• ? improvement of motor function?

• Neuroplasticity:
  - decrease of excitability of M1
  - decrease of BOLD effect
Conclusions

- Adaptive neuronal plasticity
  - Congenital hemiparesis
  - Impact of corticospinal reorganisation

- Different treatment strategies for different types of corticospinal organisation?

- Translational medicine
• Neuroplastic changes by Constraint Induced Movement Therapy
• Botulinum toxin therapy
CNS pathology

Loss of inhibition LMN

Positive features of UMN syndrome
- Spasticity
- Hyper-reflexia
- Clonus
- Co-contraction

Loss of connections to LMN (and other pathways)

Negative features of UMN syndrome
- Weakness
- Fatiguability
- Poor balance
- Sensory deficits

Musculoskeletal pathology

Muscle shortening

Bony torsion

Joint instability

Degenerative arthritis
Botulinum Toxin Type A
SV2 Is the Protein Receptor for Botulinum Neurotoxin A

Min Dong, Felix Yeh, William H. Tepp, Camin Dean, Eric A. Johnson, Roger Janz, Edwin R. Chapman

How the widely used botulinum neurotoxin A (BoNT/A) recognizes and enters neurons is poorly understood. We found that BoNT/A enters neurons by binding to the synaptic vesicle protein SV2 (isoforms A, B, and C). Fragments of SV2 that harbor the toxin interaction domain inhibited BoNT/A from binding to neurons. BoNT/A binding to SV2A and SV2B knockout hippocampal neurons was abolished and was restored by expressing SV2A, SV2B, or SV2C. Reduction of SV2 expression in PC12 and Neuro-2a cells also inhibited entry of BoNT/A, which could be restored by expressing SV2 isoforms. Finally, mice that lacked an SV2 isoform (SV2B) displayed reduced sensitivity to BoNT/A. Thus, SV2 acts as the protein receptor for BoNT/A.
Iliopsoas
Distal approach
1: M. iliopsoas 2: Caput femoris 3: A./V./J. femoris 4: M. sartorius
5: M. biceps femoris 6: M. adductor magnus 7: M. vastus medialis
8: M. rectus femoris 9: M. vastus intermedius 10: M. vastus lateralis
A way to understand CP-muscles

MRI
- PVL

Sonography
- Diameter
- Echogenicity
Identification techniques

Surrounding fascia

Neighbouring structures

Passive / active movement
Flexor carpi radialis muscle
Flexor carpi radialis muscle
Injection site
Flexor carpi radialis muscle
Transverse view

Flexor carpi radialis muscle
Transverse view

Copyright: Dept. of Handsurgery,
Alderhey Children’s Hospital,
Manchester, England
Flexor carpi radialis muscle
Transverse view - Examples

5 year old female
11 year old female
12 year old male
29 year old male
• Tibialis posterior muscle
Tibialis posterior muscle
Injection site
1: M. soleus 2: M. gastrocnemius medialis 3: M. gastrocnemius lateralis
4: M. tibialis posterior 5: Tibia 6: Fibula
Tibialis posterior muscle
Transverse view
Pattern recognition of

- contour lines and
- neighbouring structures

allows visual identification of target muscles

Active / passive movement

- allows real-time observation and identification of contraction / stretching in corresponding muscles
# Accuracy of manual needle placement

## TABLE 2. Number of Injections

<table>
<thead>
<tr>
<th></th>
<th>Number of Muscles Injected</th>
<th>Total Number of Injections (A)</th>
<th>Inaccurate Injections (B) (determined by electrical stimulation)</th>
<th>% Accuracy = (A – B)/A × 100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lower Limb</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroc-soleus</td>
<td>261</td>
<td>861</td>
<td>189</td>
<td>78%</td>
</tr>
<tr>
<td>Hamstrings</td>
<td>38</td>
<td>76</td>
<td>41</td>
<td>46%</td>
</tr>
<tr>
<td>Hip adductors</td>
<td>26</td>
<td>52</td>
<td>17</td>
<td>67%</td>
</tr>
<tr>
<td>Tibialis posterior</td>
<td>18</td>
<td>36</td>
<td>32</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Upper Limb</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>47</td>
<td>139</td>
<td>53</td>
<td>62%</td>
</tr>
<tr>
<td>Adductor pollicis</td>
<td>31</td>
<td>46</td>
<td>30</td>
<td>35%</td>
</tr>
<tr>
<td>Pronator tere</td>
<td>38</td>
<td>76</td>
<td>59</td>
<td>22%</td>
</tr>
<tr>
<td>FCR</td>
<td>15</td>
<td>30</td>
<td>26</td>
<td>13%</td>
</tr>
<tr>
<td>FCU</td>
<td>28</td>
<td>56</td>
<td>47</td>
<td>16%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>502</td>
<td>1372</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FCR, flexor carpi radialis; FCU, flexor carpi ulnaris.
<table>
<thead>
<tr>
<th>Period</th>
<th>Publication Details</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991 - 2007</td>
<td>PubMed BoNT/A / Children</td>
<td>Established, but not standardised</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Gastrocnemius muscle Injection video
Flexor carpi radialis muscle Injection video
Flexor carpi radialis muscle
Injection video
Tibialis posterior muscle
Injection video
Tibialis posterior muscle Injection video
• Real time control of injection
• Incorrect injection is no longer a matter of concern
• 27 G needles are visible
• Always use the transverse section for anatomic orientation
• Inject along the long or short axis of the transducer
## Comparison of injection techniques

<table>
<thead>
<tr>
<th></th>
<th>Palpation</th>
<th>EMG</th>
<th>Stimulation</th>
<th>Sonography</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy</strong></td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Practicability</strong></td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Speed</strong></td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Evaluation</strong></td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Future research</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Review article

European consensus table 2006 on botulinum toxin for children with cerebral palsy

Florian Heinen\textsuperscript{a,*}, Guy Molenaers\textsuperscript{b}, Charlie Fairhurst\textsuperscript{c}, Lucinda J. Carr\textsuperscript{d}, Kaat Desloover\textsuperscript{e}, Emmanuelle Chaleat Valayer\textsuperscript{f}, Edith Morel\textsuperscript{f}, Antigone S. Papavassiliou\textsuperscript{g}, Kristina Tedroff\textsuperscript{h}, S. Ignacio Pascual-Pascual\textsuperscript{i}, Günther Bernert\textsuperscript{j}, Steffen Berweck\textsuperscript{a}, Guiseppe Di Rosa\textsuperscript{k}, Elisabeth Kolanowski\textsuperscript{l}, Ingeborg Krägeloh-Mann\textsuperscript{m}
Point 6: BoNT therapy and procedures

„Use an accurate localization technique: Sonography in the pediatric population is superior to EMG or electrical stimulation.“
Common Gait Patterns: Spastic Hemiplegia

Type 1
Drop foot
\( \alpha > 90^\circ \)

Type 2A
True equinus
\( \alpha > 90^\circ \)

Type 2B
True equinus/
recurratum knee
\( \alpha > 90^\circ \)

Type 3
True equinus/
jump knee
\( \alpha > 90^\circ \)

Type IV hemiplegia
Equinus/
jump knee

Pelvic rotation, hip flexed,
adducted, internal rotation

J. Rodda and H. K. Graham, European Journal of Neurology 8 (Suppl. 5), 98±108
Pattern-orientated approach
### Safety of multi-muscle treatment

<table>
<thead>
<tr>
<th>Number of treated muscles per session</th>
<th>N≤4</th>
<th>5&lt;N≤8</th>
<th>9&lt;N≤12</th>
<th>12&lt;N≤19</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dosage per kg b.w.</td>
<td>9.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per session (Units of BOTOX®)</td>
<td></td>
<td>15.8</td>
<td>20.3</td>
<td>23.9</td>
<td>16.6</td>
</tr>
<tr>
<td>Number of sessions</td>
<td>80</td>
<td>239</td>
<td>158</td>
<td>18</td>
<td>495</td>
</tr>
<tr>
<td>Number of sessions with AE</td>
<td>4</td>
<td>21</td>
<td>15</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>Percentage of sessions with AE</td>
<td>5.0%</td>
<td>8.8%</td>
<td>9.5%</td>
<td>22.2%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

#### Severity of AE

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Not assessed</th>
<th>Discontinuation due to AE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0%</td>
<td>4.2%</td>
<td>5.7%</td>
<td>11.1%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td>4.2%</td>
<td>5.7%</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>5%</td>
<td>3.8%</td>
<td>0.6%</td>
<td>11.1%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Severe</td>
<td>0%</td>
<td>0%</td>
<td>0.6%*</td>
<td>0%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Not assessed</td>
<td>0%</td>
<td>0.8%</td>
<td>2.5%</td>
<td>0%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Multi-level treatment in a 4.5 y old boy, GMFCS IV with a total dosage of 18 U/kg b. w. For three weeks, the patient lost his ability to stand, yet no systemic, drug related adverse event was observed. The AE was considered to be a treatment related focal weakness.*

Heinen F et al., Movement disorders 2006
- Substance related AEs are rare

- Bear in mind the possibility that treatment related (biomechanical) AEs increase the more muscles are injected

- No discontinuation due to AEs
BoNT Serotype A

- **Preparation Botox®**
  - safe range [U/kg bw] 6-25
  - total dose [U] 400-600

- **Preparation Dysport®**
  - safe range [U/kg bw] 15-25
  - total dose [U] 900

- **Dilution**
  - small muscles 1-2 ml
  - large muscles 2-4 ml per vial

[U=Units; kg bw = kilogram body weight]
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