Introduction: Post-Stroke Spasticity (PSS)

- Growing base of evidence supporting the benefit of early intervention for stroke survivors\(^1,2\)
- American National Stroke Association survey: 63% of OTs & PTs reported PSS as a key reason for patients failing to meet treatment goals\(^3\)
- As PSS increases, functional independence of patients worsens\(^4\)
- Imperative to treat PSS promptly to avoid permanent disabling conditions (eg, contracture)\(^5\)
- Understanding predictive risk factors for PSS, may be helpful in planning rehabilitation for stroke patients\(^5\)

Pathophysiology of spastic paresis. II: Emergence of muscle overactivity

Positive Signs Resulting in Muscle Overactivity

- **Exaggerated tonic (spasticity) and phasic stretch reflexes (hyperreflexia and clonus)**
- **Co-contraction**
  - Abnormal antagonist contraction present during voluntary agonist effort, dependent on tonic stretch on antagonist
- **Associated reactions**
  - Abnormal contraction distant from the muscles involved in voluntary effort; contributes to synkinesia, overflow, etc
- **Released flexor reflex afferents**
  - Abnormal cutaneomotor reflexes (Babinski’s sign and flexor spasms)
- **Spastic dystonia**
  - Muscle contraction present at rest, dependent on tonic stretch

Changes related to PSS in the “Final Common Path“

Definition: Spasticity

- In every day clinical use the term spasticity is used as a collective to describe a combination of clinical signs, e.g. in Post Stroke Spasticity (PSS)

- The term spasticity was defined by J.W. Lance in the 1980s as “a motor disorder characterized by a velocity-dependend increase in tonic stretch reflex with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex as one component of the Upper Motor Neuron Syndrom” (UMNS, defined by Young 1994).
### Ashworth Scale

**Scores**

0 = No increase in tone

1 = Slight increase in tone giving a “catch” when the limb was moved in flexion or extension

2 = More marked increase in tone, but limb easily flexed

3 = Considerable increase in tone - passive movements difficult

4 = Limb rigid in flexion or extension

---

*Ashworth 1964*


### Modified Ashworth Scale

**MAS**

**Scores**

0 = No increase in tone

1 = Slight increase in tone giving a “catch” when the limb was moved in flexion or extension *less than 50% of range*

1+ = Slight increase in tone giving a “catch” when the limb was moved in flexion or extension *more than 50% of range*

2 = More marked increase in tone, but limb easily flexed

3 = Considerable increase in tone - passive movements difficult

4 = Limb rigid in flexion or extension
Early Development of PSS

- The natural time-course of PSS has rarely been evaluated
- We conducted in the South-West area around Berlin Germany a prospective, observational study (two stroke units and one Rehab Hospital) following 103 patients at a median of
- 6 days, 6 weeks and 16 weeks (>3 month) following stroke
- Evaluation:
  - Incidence of increased muscle tone
    (Modified Ashworth Score ≥1)
  - Functional disability (Barthel Index)
  - Quality of life (EQ-5D)

Wissel J, et al. J Neurol. 2010
Incidence PSS: First visit median 6 days

- 23 of 94 survivors (24.5%) showed PSS

Wissel J, et al. J Neurol. 2010

PSS: Second visit median 6 weeks

- 23 of 86 survivors (26.7%) showed PSS
- 3 survivors (3.5%) who showed PSS at first no longer did at second visit
- An additional 13 survivors (15.1%) showed new PSS at second visit

Wissel J, et al. J Neurol. 2010
18 of 83 survivors (21.7%) showed PSS.

2 survivors (2.4%) showed new PSS at 16 weeks.

10 patients (12.0%) with PSS at 6 weeks did not show PSS at 16 weeks.

98% of survivors with PSS, the condition emerged in the first weeks (about 6 weeks) following stroke.

### Characteristics of 106 Survivors with PSS:
Predictors at 16 Weeks

<table>
<thead>
<tr>
<th>Feature</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresis in affected limb</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe paresis at 16 weeks</td>
<td>0.02</td>
</tr>
<tr>
<td>MAS $\geq$2 in $\geq$1 joint within 6 weeks</td>
<td>0.01</td>
</tr>
<tr>
<td>Involvement of $&gt;2$ joints with hypertonicity</td>
<td>0.002</td>
</tr>
<tr>
<td>Hemispasticity (arm &amp; leg) within 6 weeks</td>
<td>0.01</td>
</tr>
<tr>
<td>Low Barthel Index at baseline</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Wissel J, et al. J Neurol. 2010
Predictors of PSS

Patient with high risk for PSS showed:

- Hemiparesis (arm and leg) any visit
- ≥1 joint(s) affected from PSS any visit
- low Barthel Index any visit

- Severe paresis (arm and leg) 2. visit
- MAS score of ≥2 2. visit

Wissel J, et al. J Neurol. 2010

Factors Predictive* of PSS Development

*All risk factors were shown to be significantly (P<0.05) predictive of PSS in at least one study

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Time of Onset</th>
<th>Time and Degree of PSS Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe arm paresis 2</td>
<td>Baseline</td>
<td>Spasticity by 1 month</td>
</tr>
<tr>
<td>Increased MAS 3</td>
<td>Baseline</td>
<td>Spasticity by 12-24 weeks</td>
</tr>
<tr>
<td>Low BI score 4</td>
<td>Baseline</td>
<td>Severe spasticity (MAS≥3) by 12-24 weeks</td>
</tr>
<tr>
<td>Hemihypesthesia 4</td>
<td>Baseline</td>
<td>Spasticity by 6 months</td>
</tr>
<tr>
<td>Severe paresis 4</td>
<td>Baseline</td>
<td>Spasticity by 6 months</td>
</tr>
<tr>
<td>Low EQ-5D Score 4</td>
<td>Baseline</td>
<td>Spasticity by 6 months</td>
</tr>
</tbody>
</table>

BI = Barthel Index; EQ-5D = a standardized instrument of health-related quality of life
MAS = Modified Ashworth Scale score

Factors Predictive* of PSS Development

*All risk factors were shown to be significantly (P<0.05) predictive of PSS in at least one study

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Time of Onset</th>
<th>Time and Degree of PSS Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresis</td>
<td>Any time point</td>
<td>Spasticity by 6 months</td>
</tr>
<tr>
<td>Low BI score &amp; arm/leg weakness</td>
<td>day 7</td>
<td>Spasticity by 12 months</td>
</tr>
<tr>
<td>Low BI score with left weakness &amp;</td>
<td>day 7</td>
<td>Severe spasticity by 12 months</td>
</tr>
<tr>
<td>smoking before</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low NIHSS scores,</td>
<td>patient admission</td>
<td>Spasticity by 3 months</td>
</tr>
<tr>
<td>Motricity Index retrospective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual activities</td>
<td>patient admission</td>
<td>Spasticity by 1 year</td>
</tr>
<tr>
<td>Stroke, extensive lesions in CCT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


CCT and MRI analysis: Infarct volume and involvement of sub-cortical motor pathways (cortico-spinal / reticular tract) correlates with development of PSS

- Corticospinal tract (pyramidal)
- Corticoreticular tract (parapyramidal)
- Dorsal reticulospinal tract (DRT)
- Medial and lateral reticulospinal tracts (MRT, LRT)
- Vestibulospinal tract (VST)

- Rubrospinal tract
- Tectospinal tract
- Coerulospinal tract

MAIN INHIBITORY TRACT

MAIN EXCITATORY TRACTS

1. de Cássia do Reis et al. 2008
2. Urban et al. 2010
3. Ri et al. submitted 2016
Mechanisms Leading to Increased Muscle Tone

A – Lesion of internal capsule
+ corticospinal tract lesion
+ corticoreticulare tract lesion

B: Incomplete spinal Lesion
+ tr. reticulospinalis dorsalis

C: Complete spinal Lesion
+ tr. reticulospinalis med.
+ tr. vestibulospinalis

Sheean G. 1995

PSS pattern in the upper limb
Early Management of PSS with BotulinumtoxinA

Does low-dose botulinum toxin help the recovery of arm function when given early after stroke? A phase II randomized controlled pilot study to estimate effect size.
RCT, n=30, injection within 3 weeks after stroke, UL: quarter/half dose ona-BoNTA.
MEASURES: ARAT, a&p-ROM, MAS elbow and wrist: no benefit for active treatment. Subgroup Analysis of ARAT 0 group the active groups improved (not significantly). *OnabotulinumtoxinA*

An early botulinum toxin A treatment in subacute stroke patients may prevent a disabling finger flexor stiffness six months later: a randomized controlled trial.
RCT, n=18, within 4-6 weeks, 150 u inco-BoNTA MAS significantly reduced 6 month after injection in verum. *IncobotulinumtoxinA*


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**ABCD**E Study: Asia *Botulinum Toxin-A Clinical Trial Designed for Early Spasticity- Study.*

**Design (1)**

- 163 pts. were randomly assigned (1:1 ratio) to receive *AbobotulinumtoxinA* or placebo, administered to one or more wrist and elbow muscles; dose adjustments to target muscles were permitted, dose per session up to 500 U *AbobotulinumtoxinA*
- Standard rehabilitation programs were maintained during the study
ABCDE Study: Asia Botulinum Toxin-A Clinical Trial Designed for Early Spasticity-Study.

ABCDE S Design (2)

- **Primary outcome** measure was Modified Ashworth Score (MAS) in the **most affected joint 4 weeks after treatment**
- **Secondary outcomes** evaluated changes in MAS in the other joint, Barthel Index, Modified Rankin Scale, and Functional Motor Assessment Scale scores. Pain was determined according to visual analogue scale (VAS: 0 to 100)
- **Assessments** were undertaken at baseline (first injection visit) and at **2, 4, 8, 12, and 24 weeks** post-treatment
- Patients were questioned at each study visit on adverse events (AEs)
Results (1):

- Mean duration since the stroke was 7 weeks - recorded in both treatment groups
- The three most frequently injected muscles were biceps brachii (BB), flexor carpi ulnaris (FCU), and flexor carpi radialis (FCR) muscle
- AbobotulinumtoxinA significantly improved muscle tone (elbow & wrist), as assessed by MAS scores at 4 weeks post-injection, versus placebo (mean [standard deviation] 1.73 [0.77] vs. 0.96 [0.77])

Results (2) & Safety:

- Significant improvements in MAS (most affected joint, combined joint, p<0.0001)
- Of those who reported pain (40 of 80 abo-BoNT; 34 of 83 placebo), reductions in spasticity-related pain were significantly greater than placebo at week 4 (treatment effect: −7.87) and 24 (−7.15)
- Significant improvement in passive elbow and wrist range of motion (pROM: p<0.05).
- 31 serious AEs (including three deaths; none considered to be treatment-related) and 53 non-serious AEs were reported (6% related to treatment)
- No clinically relevant differences in the distribution of AEs between Dysport (57%) and placebo (43%)
Conclusions

- Results show that BoNT-A (Dysport 500 U), combined with rehabilitation, is effective and safe in treatment of early post-stroke upper limb spasticity in Asian patients with mild-to-moderate hypertonicity and voluntary movement.

- Sustained improvements (up to 24 weeks) in muscle tone suggest that early intervention with BoNT-A aids in the prevention of more severe forms of spasticity.

PSS pattern in the lower limb
Early botulinum toxin treatment for spastic pes equinovarus – a randomized double-blind placebo-controlled study

U. M. Fietzek, P. Kossemehl, L. Schelosky, G. Ebersbach and J. Wissel

Intervention: <3 month, injection calf muscles & tibial posterior
Double-blind BoNT/A injections with a fixed dose of BoNT/A or placebo injections with an equal volume of saline (0.9% NaCl) were administered.

One leg 230 units onabotulinumtoxinA: GCM/L 60/30u, S/TP 70/70u
Two legs 460 units onabotulinumtoxinA - No guidance for injection -

Results: Patients who had received BoNT/A treatment had lower mAS compared with placebo at week 12 (P < 0.01). During the open label phase, patients from the placebo group showed further deterioration of muscle tone despite starting from a similar baseline and receiving BoNT treatment. Spastic feet that had received BoNT/A in the first cycle had comparatively lower mAS scores over all follow-up data and at week 24 (P < 0.01).

Conclusions: The study demonstrates a reduction of muscular hypertonicity in spastic pes equinovarus with BoNT/A treatment given during the first 3 months after the lesion. Exploratory analyses of the course of muscular hypertonicity during the open phase favour earlier to later treatment.

Figure 1 Flow chart of the study with number of patients and assessed feet.

- Double blind Injection
- Open Injection
Early botulinum toxin treatment for spastic pes equinovarus – a randomized double-blind placebo-controlled study

U. M. Fietzek, P. Kossmeier, L. Schelosky, G. Ebersbach, and J. Wissel

Double Blind Injection

230 units Ona-BoNT per leg

Figure 2 Mean mAS scores on weeks 0, 4 and 12 of verum treatment (black) and placebo treatment (white) groups (randomized controlled trial). Asterisks signify standard deviation. Note that mAS scores are presented as interval data with a full range of 0-5. Asterisks correspond to a Bonferroni-corrected significance level of 0.007.

End of DB study Open phase

** significant level p < 0.01

Figure 3 Mean mAS scores of the open label extension phase during weeks 12, 16, 24 and 36 of foot that received verum treatment (black) and placebo treatment (white) in the randomized controlled trial phase.
Economical Point of View

- Three class I studies 1,2,3 showed sustained improvements in spasticity (> 6 mo) from early BoNT treatment and suggest that early intervention (< 3 mo) with BoNT aids in
  - prevention of more severe forms of spasticity (MAS 3-4)
  - may prevent complications (contractures / ulcers)
  - may improve rehabilitation outcomes (active function)
- No further costs for identification of predictors of spasticity
  - Clinical markers4 (paresis, early muscle tone increase,..)
  - MRI (stroke volume5,6 and involvement of motor tracts6)
- Economical investment: Drug costs (1-3 vials of BoNT1,2,3) to early treat “increased muscle tone” following stroke


Summery I: Chronic spasticity

Significant improvement in RCTs from BoNT A treatment in body function & structure, passive (DAS) & improvement in active function (single pts.)
**Summary II:** Based on 3 Class I studies early (< 3 mo) management of PSS with BoNT A is recommended.

Sustained improvements in muscle tone suggest that early intervention with BoNT-A aids in prevention of more severe forms of limb spasticity post stroke (PSS)

Clinical Predictors: PSS
- MAS > 1 in two joints
- Severe paresis (arm&leg)
- Hemi-spasticity (arm&leg)
- Sensory deficit / Neglect
- Low BI

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Steffen Berweck & Urban Fietzek
Schön-Kliniken, Vogtareuth & Munich, Germany

Jörg Müller
Vivantes Klinikum Spandau, Berlin, Germany

Peter Koßmehl
Kliniken Beelitz, Germany
Thank you for your attention!

Prof. Jörg Wissel, MD, FRCP
Neurological Rehabilitation and Physical Therapy
Depts of Neurology, Vivantes Hospital Spandau & Humboldt Hospital,
Berlin, Germany
University of Potsdam

Upper Motor Neurone Syndrome (UMNS)

- Spasticity is one component of an UMNS, according to Lance it is defined as a velocity-dependent increase of the tonic stretch reflexes (muscle tone) with exaggerated tendon reflexes (Lance 1980, Young Neurology 1994)

- Plus symptoms
  - Increased cutaneous reflexes
  - Spasticity (Mod. Ashworth Score)
  - Mass movements / dystonia
  - Clonus
  - Abnormal postures and contractures

- Minus symptoms
  - Paresis
  - Loss of flexibility
  - Increased fatiguability
  - Sensory loss

Thilmann et al Brain 1992
Some lower-limb reflex pathways can be reliably tested in humans

Burke D, Wissel J, Donnan, GA. Neurology 2013;80:S20-S26

Vivantes is the biggest hospital chain of Germany located in one city – covering 30% of the Berlin healthcare market

Key figures of Vivantes
- 9 Hospitals in Berlin
- > 5,000 Beds
- Sales 2010 > 850 million €
- > 100 medical Departments
- 5 Neurological Departments
- 2 In-patient NeuroRehab Dept.
- 1 Out-patient Rehab center
- 14 Nursing homes
- Education and Training Facilities
- 200,000 In-patients/ Year
- 300,000 Out-patients/ Year

Locations in Berlin, Germany

Vivantes

= Neurological Rehabilitation and Physical Therapy

Source: Vivantes Corporate Development
Typical upper and lower limb pattern (posture and/or movement pattern) are combined with PSS

<table>
<thead>
<tr>
<th>Upper Limb Pattern</th>
<th>Lower Limb Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder add-/ abduction and internal rotation</td>
<td>Hip flexor / adductor spasticity</td>
</tr>
<tr>
<td>Elbow flexion</td>
<td>Proximal flexor spasms</td>
</tr>
<tr>
<td>Pronation of the forearm</td>
<td>Stiff-knee pattern, extensor spasms</td>
</tr>
<tr>
<td>Flexed wrist and clenched hand</td>
<td>Plantar flexed and inverted foot (pes equino-varus)</td>
</tr>
<tr>
<td>Thumb in palm, intrinsic hand muscle stiffness</td>
<td>Clawed toes &amp; hitchicker’s grandtoe</td>
</tr>
</tbody>
</table>

What is Spasticity?
Spasticity, an impairment that is poorly defined and poorly measured.

Malhotra S et al.

In summary, it is reasonable to conclude that there is no adequate definition of the phenomenon of spasticity.

Table 1 Definitions of the term 'spasticity' used in the literature

<table>
<thead>
<tr>
<th>Measure used</th>
<th>Lame</th>
<th>Muscle Tone</th>
<th>None</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trials</td>
<td>59</td>
<td>62</td>
<td>58</td>
<td>4</td>
</tr>
<tr>
<td>Literature reviews</td>
<td>16</td>
<td>13</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Case reports</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>78</td>
<td>88 (21%)</td>
<td>78</td>
<td>6 (1%)</td>
</tr>
</tbody>
</table>

This table demonstrates that the most common definition for spasticity equates the phenomenon with 'muscle tone' and that a significant number of articles have not provided an explicit definition for the phenomenon.

Clinical Assessment: Increased Muscle Tone

- Spasticity: velocity-dependent increase in tonic stretch reflex

Passive Stretch: Enhanced EMG-activity = Increased Resistance

Thilmann et al. 1992
Hypokinetic (Impairment of movement)
- Spasticity
- Static spastic dystonia
- Spastic co-contractions

Hyperkinetic (Involuntary movement)
- Spasms (flexor, extensor, adductor)
- Associated reactions
- Mass movements
- Action-induced spastic dystonia

Mechanisms of increased muscle tone = PSS in hemiplegia

Burke D, Wissel J, Donnan, GA. Neurology 2013;80:S20-S26
European SPASM Consortium

‘Disordered sensori-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles’

Spasticity: Clinical perceptions, neurological realities and meaningful measurement

A. D. Pandyan\textsuperscript{1}, M. Gregoric\textsuperscript{2}, M. P. Barnes\textsuperscript{3}, D. Wood\textsuperscript{4}, F. Van Wijck\textsuperscript{5}, J. Burridge\textsuperscript{6}, H. Hermens\textsuperscript{7}, & G. R. Johnson\textsuperscript{4}

2005

Current Treatment Options in PSS

- Exercise and physical modalities
- Systemic drugs
- Chemodenervation: e.g. BoNT A
- Intrathecal drugs: e.g. Baclofen
- Neuro-orthopaedic and Neurosurgical methods
The efficacy of Botulinum Toxin A for spasticity and pain in adults

A systematic review and meta-analysis

Objectives: A systematic review and meta-analysis using the Grades of Recommendation, Assessment, Development & Evaluation (GRADE). All RCTs on adults with spasticity of any origin in the upper or lower limb, treated with a single dose of BoNT A, with outcome measures for pain or spasticity (only: body structure & pain).

Results: A total of 37 studies were reviewed. A meta-analysis was carried out on 10 for pain and 21 for spasticity. Evidence quality was low/very low for pain. No significant effect was found in UL (SMD=0.44, CI -0.02 to 0.90, Z = 1.88, P=0.06), and in LL (RR = 1.01 CI 0.19 to 5.36, Z = 0.02, P=0.99).

Evidence quality for spasticity was moderate. Significant effects were found in the UL (WMD=0.88, CI 0.63 to 1.14, Z = 6.86, P<0.00001), and LL (RR=2.42, CI 1.60 to 3.65, Z=4.18, P<0.0001).

Conclusion: The use of BoNT A is supported for UL & LL spasticity. Further evidence is needed for spasticity-related pain.

Summery III

BoNT A

Multi-Professional Treatment

MTD & goal setting

Physical Methods Surgery

Integrated