Pathophysiology of Spasticity and Therapeutic Approach

Jörg Wissel

1 Introduction

It is well known that with a delay a lesion of the central nervous system (CNS) involving senso-motor networks in the brain or cervical or thoracic spinal cord will lead to an Upper Motor Neuron Syndrome (UMNS) caudal of the lesion. Clinically UMNS could be detected by increased resistance against passive movement during rest position (defined by Lance [22]), enhanced tendon reflexes [12, 28, 38], pyramidal signs and flexor-reflexes [12, 28], Co-contraction [12, 38], spastic dystonia [12, 38], and result in disturbed posture, slowed motor performance with decreased dexterity and coordination difficulties named spastic movement disorder (SMD, [13]).

In every day communication clinicians use the term "spasticity" as a collective to describes a motor syndrome that include positive and negative symptoms reflecting the UMNS of which spasticity defined by Lance [23] is only one part. The Lance 1980 definition describes the phenomenon only with its reflex features during rest, and that is not enough to reflect the burden of SMD.

Therefore it is of major importance to include all positive features of UMNS that may be part of SMD during voluntary and involuntary movements in the definition to allow those as targets for future management or training programs to better reduce motor coordination difficulties and slowing of voluntary movement as main activity limitation features of SMD [14].

J. Wissel (✉)
Department of Neurology, Department Neurological Rehabilitation and Physical Therapy, Vivantes Hospital Spandau, Neue Bergstrasse 6, 13585 Berlin, Germany
e-mail: Joerg.Wissel@vivantes.de

G. Sandrini et al. (eds.), *Advanced Technologies for the Rehabilitation of Gait and Balance Disorders*, Biosystems & Biorobotics 19,
https://doi.org/10.1007/978-3-319-72736-3_30

It is estimated that at this time point more than 12 million people worldwide suffer from SMD of different severity [21, 55]. In those people UMNS can be caused by a variety of diseases such as ischemic stroke of the brain or spinal cord, brain or spine hematomas, traumatic brain (TBI) or spinal cord injury (SCI), brain or spinal cord tumors, multiple sclerosis (MS), inflammation or infection of the brain or spinal cord, spastic cerebral palsy (CP), neurodegenerative diseases like Amyotrophic Lateral Sklerosis (ALS) or hereditary disorders like Hereditary Spastic Paraplegia (HSP).

With respect to ongoing discussion on how we should handle spasticity in early stages of diseases common ground in clinical neurology is that acute causal treatment of underlying disease should be completed or finished (e.g. systematic thrombolysis in stroke or antibiotics or virostatic treatment in encephalitis), causal treatment should be on an established therapeutic level (e.g. immune modulation in MS) or not available (e.g. in HSP) to allow the team to focus with therapeutic intervention on the management of SMD only. Nowadays in most patients with lesions of the CNS (e.g. more than one week following stroke, TBI, SCI) there is no option of further causal treatment of the remaining symptoms, but it is of major importance to introduce preventive measures to avoid another stroke like secondary prevention following stroke (e.g. introducing anticoagulation in cardiogenic stroke) or treat risk factors for further insults (e.g. treat cardiac valve defects, metabolic disease or arterial hypertension) or avoid consequences of chronic sequelae (like contractures or skin damage from severe spasticity).

The exact prevalence of UMNS with clinically relevant positive features that can be classified as spasticity is not known. However, it is estimated that up to 40% of stroke [51] survivors and more than 50% of patients with MS and CP are affected by increased resistance against passive movement during rest position [23] throughout the cause of their disease. This implies that in industrialized countries—with increasing numbers of elderly inhabitants and increasing numbers of stroke and cancer survivors and countries with well organized intensive care units with higher numbers of survivors of severe CNS lesions (TBI and SCI)—the consequences of spasticity create an increasing social and economical burden and triggers increased efforts to better understand and manage SMD [55].

2 Clinical Signs and Definition of Spasticity

Unfortunately in the last 30 years the term spasticity has been inconsistently defined [27]. Nowadays consensus among specialists in basic science and clinical management in the field of spasticity research is that spastic muscle tone defined as increased resistance against passive movement during rest position is only one of several components of the UMNS that form the clinical syndrome spasticity [13, 32].

Spasticity definition by Lance [23] focuses on spinal reflexes during rest position and not on disturbed voluntary movement performance in UMNS and defines spasticity as a motor disorder, characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as one component of the UMNS during rest position. Passive stretch of a spastic muscle during rest position, if monitored by surface electromyography (sEMG), produces increased sEMG activity while slow stretch velocities than in normal controls or compared to sEMG recordings in the same condition (angle velocity constant) from non affected muscles [43]. Therefore in case of spasticity defined by Lance [23] and the other positive symptoms/signs of the UMNS like clonus, co-contraction of antagonists or spastic dystonia higher amounts of sEMG activity can be registered from involved movement segments (antagonistic muscles) than in segments that are not affected from UMNS when passively stretched.

Other positive features of UMNS than velcocity-dependent increase in muscle tone are hyperreflexia (increased amplitude of tendon reflexes and increased area where the tendon reflexes can be elicit), muscle hypertonia (increased baseline muscle tone/activity), co-contraction of antagonistic muscles (disturbed antagonistic coordination, mainly inhibition of antagonist is diminished), associated reactions and disinhibited movement synergies [14].

The SPASM Consortium (European Thematic Network to Develop Standardized Measures of Spasticity [32]) put together 2005 a new definition: Spasticity is defined as a disordered sensorimotor control, resulting from an upper motor neuron (UMN) lesion, presenting as intermittent or sustained involuntary activation of muscle. That definition excluded all negative features from UMNS (see above) and secondary changes like soft tissue shortening, contracture and bony changes from definition of spasticity. Therefore as described above spasticity represents only involuntary muscle activation that could be induced by stretch, voluntary movement or other triggers. Those spastic activity could be spontaneous—intermittent (like spastic dystonia without trigger [12, 38], or e.g. sustained muscle activity following stretch (with trigger, e.g. pyramidal signs and flexor-reflexes [12, 28]) or Co-contraction [12, 38], that create spastic posture or movements in body segments affected from the UMNS.

Based on this definition it is possible to clinically classify the topical distribution of spasticity over the different body segments affected from UMNS [50]. With respect to the topical distribution of involuntary muscle activity that fulfill the SPASM definition a focal (one hand, one foot or elbow) or multi-focal (hand and foot) distribution can be differentiated from segmental spasticity (two or more focal areas beside to each other are affected e.g. segmental arm-spasticity: hand and forearm with elbow or segmental leg-spasticity: toes, ankle, knee and hip is involved) or multi-segmental (both legs: para- or leg and arm on one side: hemispastic), and generalized distribution of spasticity (e.g. all four limbs and body is affected) [50].

Using neurophysiological measures with poly-s-EMG (surface-Electromyography) to monitor muscle activity at standardized electrode position over multiple muscles (poly-s-EMG) at upper and lower limb and core muscles during different body positions and action it is possible to document SMD [54]. While recordings at rest, when eliciting mono- and polysynaptic reflexes, and during a protocol of standard passive and active motor tests/tasks e.g. alternating passive and active extension and flexion of joints, in the body segment affected from UMNS the negative and positive symptoms of the UMNS could be registered as increased and/or un-coordinated tonic or phasic EMG activity in antagonistic muscles (for method see Brain Motor Control Assessment = BMCA) [39]. This highly standardized evaluation procedure BMCA with poly-sEMG recordings allow to classify the different spastic motor patterns and positive clinical features of UMNS on the basis of poly-sEMG registration in cerebral and spinal lesions.

In case of instrumented gait analysis with poly-sEMG of leg muscles and additional registration of kinematic parameters of hip, knee and ankle and kinetic parameters (force platform) it allows to classify spastic gait pattern (e.g. co-contracting activation pattern of rectus femoris during swing phase in stiff knee gait pattern) [5].

Biomechanical changes of muscle properties in the region affected from UMNS are believed to begin with delay from the CNS lesion [13]. Over time body segments affected from spasticity show muscle atrophy and increased muscle stiffness (increased inertia of the muscle) as well as soft tissue (fascias and tendons) shortening that ends up in muscles and soft tissue contractures that are clinically named spastic contractures. Spastic contracture can begin few hours after the onset of immobilization following CNS lesion [14]. Progressive shrinking of muscles and soft tissue may result in restriction in passive and active Range of Motion (pROM and aROM) of joints and whole limbs involved which add to the spastic movement patterns and spastic postures and limbs disfigurements [50].

Muscle atrophy may be due to loss of voluntary activation [31] or by reduced stretching and loss of sarcomers that was found in muscle biopsy [25].

Negative features of the UMNS are muscle weakness or paresis (reduced ability to voluntarily develop adequate muscle force in intended—selected muscles), generalized fatique (loss of ability to produce adequate levels of motor activity), loss of dexterity (incoordination of fine motor tasks), loss of flexibility (inability to fast react with senso-motor system to external irritations) and disturbed fine motor tasks or falls coordination of movements [13, 14].

Features of these negative symptoms of the UMNS like e.g. paresis, fatique and disturbed coordination of fine motor tasks result in the opposite features in sEMG compared to those of the positive features of the UMNS. Usually in paretic muscles less amount of voluntary sEMG activity could be generated by the patient in movement segments involved in UMNS and less well coordinated sEMG activity can be registered in case of multi-sEMG recordings from antagonistic muscles affected from the UMNS compared to multi-sEMG recordings from movement segments non involved in an UMNS [5, 39].

In case of spastic paresis or SMD voluntary single joint movements are characterized by a combination of weak force generation (paresis, measured clinically with the Medical Research Council scale, MRC scale) and changes in movement coordination (disturbed reciprocal inhibition) which can be described in kinematics as disturbed (reduced velocity and coordination) intended trajectories compared with trajectories produced by normal controls [1].

Typical changes in kinematic parameter of ballistic single- or multi-joint movements in patients with SMD compared with normal controls are performed in a reduced movement velocity and disturbed velocity and acceleration profile representing and mirroring the clinical impression of uncoordinated and slowing of fine motor task performances in patients with spastic limbs and SMD.

In SMD movements directed against the direction of increased spastic muscle tone (spasticity defined by Lance [23]) are altered by a higher quantitative resistance around the joint that should be moved than usually generated in normal movement without spasticity. This increased resistance could result from joint stiffness from neural origin, e.g. from hyper-reflexia or increased muscle tone (Lance [23] definition) and/or non-neural origin, e.g. increased tissue visco-elastic resistance and contractures resulting from soft tissue or muscle shortening [7].

The primary neuronal network features of the UMNS as well as the secondary changes e.g. contractures are the driving factors that cause decreasing ability to manage daily activities and mobility, reduced comfort while sitting and promote spasticity-associated pain. Therefore beside paresis, which always is focused by patients, caregivers and sociaty (negative feature of the UMNS) spasticity defined by Pandyan et al. [32] and spastic contractures (shortening of muscles and soft tissue involved) has a substantial negative impact on patients' and caregivers' quality of life [50].

Coming from a patient centric approach in neurorehabilitation spasticity should be characterized as an individual combination or mixture of positive symptoms of the UMNS in certain topical distribution that causes a characteristic SMD. Nowadays it is consensus among physicians and therapists in the multiprofessional team that the way of staging the different symptoms and consequences of spasticity is to use reliable and valid clinical measures like scales or scores and if possible (patient or caregiver agreement) to videotape the individual SMD during standard motor tasks (e.g. sitting, standing, walking, reaching an object and drinking from a cup of water) [8, 50]. It is recommended to capture beside the personal goals for treatment [46] the level of impairment (e.g. p- and a-ROM, muscle tone with AS, REPAS or MAS, spasticity and co-contraction with Tardiue scale in every movement segment involved in spasticity), the level of activity limitations in the upper limbs (UL) and lower limbs (LL) and evaluate of quality of life (QoL) with established questionnaires as well as carer burden (if any) and participation to fulfill the standards of the International Classification of Functioning (ICF) [50].

The minimum standard of communication in between specialized centers should include upper limb (UL) and lower limb (LL) muscle tone (AS/MAS/REPAS), paresis (graded with BMC scale) and p-ROM (Neutral-0-Methode) as well as

evaluation of voluntary movement capacity (a-ROM and defined motor tasks in standardized test manuals, e.g. nine-howl-peg-test or the box and block test) in limbs involved in UMNS, activities of daily living (ADL scales e.g. the Barthel or FIM) as well as quality of life information (QoL, e.g. EQ5D or SF36) and in a descriptive way social and professional participation.

3 Pathophysiology of Spastic Paresis

It is believed that reflex features of spasticity and disordered motor control in SMD result from altered balance of inputs from reticulo-spinal and sub-cortical descending pathways supplying the anterior horn cells pool (Sherrington path) and inter-neuronal circuits at spinal cord levels and not from isolated lesion located in the primary motor cortex that origin the cortico-spinal or pyramidal tract [37].

The absence or disturbance of cortico-spinal tract information that project directly to anterior horn cells (tractus corticospinalis anterior and lateralis) also seems to be of major importance in the concept of a dysbalance and loss of descending tonic or phasic excitatory and inhibitory inputs projecting to the spinal sensorimotor networks and therefore alter segmental spinal balance of excitatory and inhibitory control from supraspinal drive [4].

A CNS lesion involving sensorimotor cortical and subcortical motor areas and tracts of the brain or brainstem may disturb the balance of supra-spinal inhibitory and excitatory input to the segmental and multi-segmental spinal mono- and polysynaptic reflexes and anterior horn cells and may produce spontaneous muscle activation or co-contraction (spastic dystonia) of antagonistic muscles as well as disturbed reciprocal inhibition of antagonistic muscles and create with a certain delay from the start following the lesion a so called cerebral spasticity pattern [13, 14].

Altered abnormal efferent drive from residual motor areas or tracts often result in characteristic spastic co-contraction from disturbed reciprocal inhibition or dysbalance of efferent motor drive to antagonistic muscles. Therefore this spastic co-contraction is a phenomenon of supraspinal origin and is defined as an excessive degree of antagonistic activation in response to voluntary agonist command [47]. This pathological co-contraction originates from the lesion in the brain or is compensatory and produces misdirection of supraspinal descending pathways, particularly from the brainstem region, resulting in pathologically co-activation of antagonistic muscles [13, 14].

The dysbalance of supra-spinal input to segmental interneuron network supplying anterior motor horn cells is producing a state of disorganization of voluntary activation and disinhibition of the spinal reflexes. These include the stretch reflex, the nociceptive polysynaptic reflexes and the withdrawal reflexes and extensor reflexes. This disinhibition of mono- and polysynaptic reflexes create a disabling situation of hyperactive spinal reflexes (e.g. increased sensitivity of tendon-reflexes, decreased inhibition of nociceptive reflexes and increased reflex amplitudes of mono and polysynaptic reflexes), while other positive symptoms are related to

disordered control of voluntary movement from abnormal efferent motor drive to the anterior motor horn cells. With respect to the performance of voluntary movements it seems that a major factor is the overall involvement of antagonist coordination, especially the aspect of disturbed reciprocal inhibition and the resulting resistance to voluntary movements [4].

Typical limb postures in chronic spasticity e.g. following stroke are coined as spastic patterns and in more than 90% of these patients with post stroke spasticity show spastic flexion pattern in the UL (spastic flexion of the elbow and wrist) [18] and spastic extension pattern in the LL (spastic stiff knee and pes equines). Spastic dystonia is of supra-spinal origin and the main driver of such spastic postures and contribute to contracture, pain and deformities [15].

Spastic dystonia is characterized by tonic muscle activation of antagonistic muscles around joints and the amount of muscle mass involved add to typical postures (muscle mass of flexors in UL and extensors in LL is bigger than antagonists). These spastic limb pattern has negative consequences on body image and self perception, and patients tend to desire a more natural and relaxed limb position in public and consider this as a relevant goal for focal spasticity treatment e.g. with Botulinum Neurotoxin [50].

In patients with spinal cord lesions e.g. in the cervical and upper thoracic levels these disturbance included dysbalance of supra-spinal inhibitory and excitatory inputs to the spinal reflexes and caudal from lesion a dis-inhibition of spinal automatisms e.g. so called stepping automatism from a spinal stepping generator in the disconnected lower thoraco-lumbal myelon. This may be an additional feature of spinal cord lesions compared to cerebral disconnecting features and justify naming this somewhat different clinical picture as spinal spasticity [7].

Disturbance of active movements in SMD (spastic movement disorder) result in major parts from disturbed antagonistic coordination and not from paresis. Active movements against spastic force (from an spastic antagonist) generated from an agonist directed against the spastic antagonist are disturbed by a lack of inhibitory command to the spastic antagonist muscle resulting from a falls coordination of motor commands on the spinal level that originate from falls supra-spinal commands that origin from the damage of cortical, subcortical or spinal sensorimotor areas or tracts. Other positive symptoms that result from this dysbalance on spinal level in the UMNS also include muscle tendon hyperreflexia and clonus, increased tonic stretch reflexes (muscle tone increase), the clasp-knife phenomenon, flexor and extensor spasms, and spastic co-contractions, associated reactions and spastic dystonia [15].

Negative symptoms result from lesion of the motor cortex, sub-cortical ganglia and descending motor tracts (pyramidal and para-pyramidal tracts) in the brain and spinal cord that result in lack of directed excitatory activity to targeted anterior horn cell cohorts for intended movements and create an unbalanced excitatory and inhibitory descending command to sensorimotor spinal networks and result in weakness (paresis), central fatique and lack of motor co-ordination.

Positive and negative symptoms of the UMNS are caused by a CNS lesion, whereas it is believed that biomechanical changes are secondary and occur with

delay from the insult. It is well known that every individual with an UMNS show an individual combination of direct consequences from CNS lesion called positive and negative features and secondary changes as a result of spontaneous remission and management of the symptoms and complications that can occur during the chronic phase of spasticity.

4 Therapeutic Approach

The primary goal for management of spasticity is maximal independence in life for patients affected from SMD. Therefore especially in the acute and post-acute phase of the management of spasticity (during the neurorehabilitation phase) a combination of different symptomatic non-pharmacological and adequate pharmacological treatments with low risk of side effects and an individualized self-stretching and re-learning program of basic motor skills that allow improved mobility (such as standing, transfer, walking) and self care (such as washing themselves, eating and dressing) should be applied. The ultimate goal for managing the chronic phase of spasticity would be to gain the best improvements in activities of daily living as possible to reach maximal quality of life and best re-integration into prior professional and social life possible. As each patient has individual disease and specific combination of positive and negative symptoms of the UMNS and complications (muscle shortening, contractures) the management program should aim for SMART-goals (S = specific for the patient, M = measurable, A = attainable and action orientated, R = realistic and relevant, T = time sensitive, time bound) [50].

Adequate management of spasticity requires multi-professional team of specialized therapists (physio- and occupational, language and swallowing therapists, sports- and training therapists, rehabilitation nurses and social workers) in an adequate setting (in- or out-patient facilities) under supervision and lead of a specialized head-physician with education in neurorehabilitation, neurology or physical medicine and rehabilitation and long standing experience in the management of spasticity. An additional team of adjunctive specialized physicians (neurosurgeon, orthopedic or plastic surgeon, ENT-physician, ophthalmologist and so on) should also be available and if needed part of the specialized spasticity management team [8, 50].

In the beginning of the management process it is of major importance to include patient and if adequate caregivers in the process of appropriate goal setting for the treatment. Appropriate treatment goals should be SMART (see above) and should help to reinforce communication in between patient and the multi-professional team. Such SMART goals allow to bring patient and multiprofessional team activities to synergistic rehabilitation efforts and allows to adapt spasticity management strategies according to the patients abilities to overcome restrictions from SMD [45, 48].

4.1 Management Strategies

A variety of treatment options for spasticity are available. Selection and sequence of the specific treatment measures for individual patient suffering from UMNS should be based on thorough clinical evaluation and multiprofessional—and if adequate interdisciplinary—team decision. Clinical experience has shown that a so called parallel multi-modal approach to spasticity management using different measures/tools in the same time frame for treatment of SMD has many benefits for the patients, e.g. combining physical therapy with pharmacological and/or surgical treatments [8, 26, 49, 50].

4.2 Assess Spasticity to Implement Individualized Management Strategy

To implement an optimal individualized management program first step is accurate assessment of muscle tone, range of motion, spasticity features and functional impairment. Nowadays it is consensus among physicians and multiprofessional team that the best way of staging the different symptoms and consequences of spasticity is to use reliable and valid scores and scales and to videotape the SMD if patient agrees and gives informed consent for it. It is recommended to document on the different levels of the ICF and gain information on the level of impairment (pROM, Modified Ashworth scale, Tardiue Scale), level of activity limitation and dexterity as well as quality of life (QoL) and participation levels. It is of major importance to cover all levels and domains of the International Classification of Functioning (ICF) [8, 50]. Several scales are introduced to assess SMD.

4.3 Muscle Tone

Ashworth Score (AS) [3], Modified Ashworth Sore (MAS) [2] and the Resistance to Passive Stretch scale (REPAS) [34] are well established to communicate the degree of muscle tone increase among clinicians. They are widely used in epidemiological and interventional studies to clinically score this feature of SMD. In this scores (AS, MAS and REPAS) higher numbers of the score values represent more marked muscle tone increase when passively stretch muscles of a movement segment/joint during rest position. AS and MAS counts from 0 to 4, with additional +1 in between 1 and 2 in the MAS. 0 represents no, and 4 the maxim of muscle tone increase (severe increase in muscle tone). A highly standardized form of scoring muscle tone increase in all limbs at one time point is established with the Resistance to Passive Stretch scale (REPAS scale). This scale allows documentation of the

distribution of muscle tone increase and therefore takes topical aspects of spasticity distribution over the different body segments (e.g. focal, segmental, hemi-, para-, generalized spasticity pattern) into account and allows to detect changes in muscle tone distribution following interventions in regions that was not focally treated [34]. However, AS, MAS and REPAS only measures muscle tone increase and not disturbance of active movement from spasticity and the impacts on loss of activity and function from spasticity, that affects patient's lives. To measure consequences on activity and participation from UMNS other instruments have to be used [33].

4.4 Range of Motion

In normal controls every single joint of the body could be moved in a passive and active manner to a certain degree. Every joint with normal anatomical conditions of bones, joint capsula, ligaments and muscles as well as soft tissue can be moved in a certain range of motion (ROM: normal values for every joint available in the literature). Therefore these ROM could be clinically evaluated with respect to its passive range of motion (p-ROM) or active range of motion (a-ROM).

An established form of documentation of the p-ROM and a-ROM (e.g. the elbow joint) is the Neutral-0-Methode. Intrapersonally the p- and a-ROM usually is the same as the muscles are physiologically strong enough to move the howl range of motion and therefore no contractures can be established (e.g. for the elbow a normal ROM would be described as 10° extension and 130° flexion of the elbow. Documentation of ROM with respect to rules of the Neutral-0-Methode: 10/0/130). In a patient with e.g. acute paresis of the elbow flexors due to stroke (minus symptom of the UMNS) a-ROM could be less for elbow flexion than p-ROM (e.g. p-ROM 10/0/130 and a-ROM 10/0/90: Paresis result in decrease of active elbow flexion from p-ROM 130° to a-ROM 90°). In a patient with chronic spastic paresis and established contractures (chronic spasticity) in extension and flexion movement of the elbow a- and p-ROM could be reduced compared to normal values (e.g. p-ROM 0/10/90: 10° extension movement is not possible/no 0° passively reached, maximum passive extension—stretching is 10° flexion/maximum flexion 90° flexion; a-ROM 0/40/60: active extension only to 40° of flexion position and active flexion to 60° flexion of the elbow, no 0° reached).

Unfortunately in chronic phase of spasticity many patients develop shortening of muscles and soft tissue in joints/movement segments involved in SMD. E.g. in post stroke spasticity (PSS) more than half of the patients affected from spasticity developed at least one restriction in passive range of motion (p-ROM) of joints involved. Restricted ROM from spasticity result in immobility and discomfort when sitting and sleeping, and create difficulties with skin care and hygiene that may lead to skin lesions and pressure source [8, 50]. Reduced ROM in combination with clinical features of the UMNS in the same joint should form the clinical diagnosis

of spastic contracture. If contractures include multiple joints of spastic limbs this may result in typical spastic upper limb deformities [18] or spastic gait patterns [5].

4.5 Spastic Paresis: Muscle Force Decrease and Disturbed Reciprocal Inhibition

With respect to the performance of voluntary movements it seems that one major component of the SMD is the overall involvement of antagonist coordination, especially the aspect of disturbed reciprocal inhibition and the resulting resistance to voluntary movements against a spastic antagonist. The most adequate scale to cover this aspects of the positive features of the UMNS is the Tardieu Scale (TS). A systematic review of the value of the Tardieu Scale for the measurement of spasticity confirmed that statement [17].

To cover the aspect of paresis it is recommended to test muscle force of involved body segments and include the Medical Research Council scale (MRC scale) for scoring of paresis in all movement segments included in spastic paresis. In case of SMD voluntary single- or multi-joint movements are characterized by a combination of weak force generation (paresis from decreased ability to activate adequate number of anterior horn cells, measured clinically with the MRC scale) and disturbed coordination of muscles involved in terms of disturbed reciprocal inhibition and disturbed synergistic muscle activation (scored clinically with the Tardiue scale).

Movement performance in SMD can be captured and quantified by kinematic analysis of single- or multi-joint movements. Typical changes in kinematic parameter of ballistic single—or multi-joint movements in patients with SMD compared with normal controls show reduced movement velocity and disturbed velocity and acceleration profiles (increased numbers of velocity and acceleration changes per trajectory/stroke) representing and mirroring the clinical impression of slow un-coordinated (discontinuous) motor task performances [9]. As a consequence of UMNS voluntary movement of the agonist (e.g. extensors of the wrist) directed against the resistance of increased spastic muscle tone produced by the antagonist (e.g. flexors of the wrist and fingers) due to loss of antagonistic inhibition or due to resistance from other neuronal (e.g. clonus, disinhibition of tendon reflexes [13, 14]) or non-neuronal joint stiffness (e.g. increased visco-elastic resistance of muscles and soft tissue [25, 31]) the numbers of changes in velocity and acceleration in the profile for spastic movements against spastic antagonists increases and reflect the loss in dexterity and coordination of fine motor tasks.

Spastic paresis with all these neuronal network features of the UMNS (paresis and disturbed reciprocal inhibition) as well as secondary changes e.g. contractures are the most driving factors for reducing levels in activities of daily activities (ADL) and participation and create more need for caregiver assistance and decrease levels of mobility and promote spasticity-associated pain. Therefore beside paresis, which always is the focus of the patients and caregivers (negative feature of

UMNS) spasticity (all positive features of UMNS) and spastic contractures (consequence of spasticity with shortening of muscles and soft tissue combined with spastic features in the same movement segment) has a substantial negative impact on patients' and caregivers' quality of life [55].

4.6 Spastic Contracture

Using the terminology spastic contracture for restriction in p-ROM in the context of an UMNS does not allow to differentiate whether the spastic contracture is caused by increase in muscle tone, co-contraction, spastic dystonia or disinhibited movement synergists and associated reactions or whether the contracture result from paresis of agonist muscles or chronic false positioning of the limb [13, 14].

As a result from the individual CNS lesion that create an individual mixture of positive and negative features of the UMNS and spontaneous (as a result of the UMNS) or correlated with additional factors, like e.g. neuropathic pain or shoulder hand syndrome (complex regional pain syndrom) visco-elastic changes in spastic muscles and surrounding soft tissue arises and create a certain force of a spastic torque imbalance around the spastic joint involved and lead to spastic joint position. With time and without positioning in stretched position shrinking of soft tissue increases to spastic contractures (loss in normal stretched positions, normal pROM) and may result in spastic upper and lower limb deformities, e.g. called typical spastic upper limb pattern following stroke [18].

4.7 Prerequisite Before Starting Symptomatic Spasticity Treatment

Before specific treatment for spasticity should be initiated the absence of so called spasticity triggers or triggering factors that promote spasticity (e.g. local skin irritation, local pain or pressure ulcer, bladder infection, and so on) should be confirmed or excluded [49]. If no trigger factors can be identified start of the management should be made by an adequate nursing regime with positioning of the spastic limbs in mild stretch position [50].

4.8 Physical Treatment Modalities

The most important physical management strategy is lengthening of muscles involved in spasticity. Stretching activity for at least 30 min a day should be started as soon as possible following CNS lesion to avoid spastic contractures [44]. If

spasticity and restriction in p-ROM is evident long lasting stretching is recommended (minimum 6 h a day [1]), therefore positioning techniques in bed or wheelchair, splinting, casting or bracing of spastic limbs are recommended to increase time in adequate stretching position. Beside passive, active stretching by activation of antagonist muscles and stretching from postures (standing in a tilt table or a frame) or positioning of limbs in standardized positions are also recommended as self training or training activities with relatives or care givers [15].

The role of physical treatment measures (physio-, sports- and occupational therapy, training therapy and robot based movement therapy) alone or in combination with Botulinum Neurotoxin injections (see below) in the management of post stroke spasticity (PSS) is established in national and international guidelines and form the basis for meaningful improvements in the management of patients suffering from spasticity features and their consequences in every day clinical practice [8, 50].

The combined treatment approach of physical treatment in physio- and occupational therapy or robot-based repetitive training of agonist muscles and Botulinum Neurotoxin injections of spastic antagonistic muscles with the option of re-training of reciprocal inhibition should include alternating movements of different velocities in maximal amplitude to reduce muscle co-contraction and therefore re-educate motor-coordination [50]. This repetitive performance may help to reduce spasticity, avoid contractures and re-establish reciprocal activation and inhibition on a spinal level. Intensity and repetition rate of exercises can be enhanced effectively by using robotic devices or support motivation with virtual reality. This may allow more active movements and increase therefore repetition rate per day [24].

With respect to gait training following e.g. incomplete spinal cord injury or brain lesions (e.g. stroke) it is evident from controlled studies (see Chapter) that increasing number of steps per day above a certain level (level that should be reached seems to be more than 500 steps per day) and introducing training in real context of walking (verticalisation together with coordinated leg movements) results in faster re-learning of walking capacity [19]. Current data on available technological approaches that use high-intensity and repetitive task-specific practice with high number of movement repetitions indicate that better results of re-learning of active movements are achieved in the lower leg and the arm than in the hand [24].

Virtual reality (VR) rehabilitation-based therapy has also shown to promote improvements in SMD by using simple computer games representative of daily activities of self-support. This new therapies applied in a multiprofessional team approach for spastic paresis has demonstrated clinical value, although the underlying changes in neuronal reorganisation supported by VR are still not clear.

Therefore if positive features of UMNS occur and alters physical therapy or robot-based training or VR rehabilitation injection of Botulinum Neurotoxin Type A (BoNT-A, see below) may help to decrease restrictions in training from increased muscle tone in certain antagonistic muscles and improve co-ordination of antagonists and will allow the patient to continue with high intensity repetition training using robotic or VR devices or a self rehabilitation training approach.

4.9 Botulinum Neurotoxin Treatment of Focal and Segmental Spasticity

BoNT-A is treatment of choice for focal, multifocal and segmental spasticity [40, 42]. BoNT-A has a grade A recommendation from the American Academy of Neurology for the treatment of focal spasticity in adults and children. There is ample evidence that BoNT-A significantly decreases muscle tone and improves passive function. The demonstration of functional gains in terms of active function has proved to be more difficult but reached statistical significant levels in a systematic review for the spastic upper limb [11] and could be nicely shown in a controlled randomized trial in chronic stroke patients published by Gracies [15, 16]. However, combining toxin injections with active physical therapy has shown functional improvements, lending support to the concept that the howl management of spastic paresis should be part of a comprehensive spasticity service and included in a multi-professional team approach [8, 50].

4.10 Mechanism of Action Botulinum Neurotoxin

The chlostridial toxin named Botulinum Neurotoxin Type A and B (BoNT-A and -B) acts in vertebrates at the level of the synapses (e.g. connecting point between the nerves and the muscles: motor endplate). Following intake into the body of a vertebrate (e.g. intramuscular injection) BoNT-A enters the cholinerge neuron in the region of the terminal axon membrane. By blocking the ability to fuse intracellular vesicals filled up with Acetylcholine with the synaptic membrane BoNT-A induces in intoxicated neurons a dose dependent blockade of cholinergic transmission and led to a clinically flaccid paresis by so called chemodenervation of cholinergic motor endplates to both extrafusal and intrafusal muscle fibers.

Nowadays the molecular mechanism is much better understood. Following entering the body e.g. BoNT-A is bound to specific receptors called SV-2 that are exposed at the outer surface of the nerve cell when vesicles are fused with the membrane. If BoNT-A is bound to the SV-2 receptor it enters the terminal axon by transportation into the cytoplasma and blocks specific proteins (SNAP-25) necessary for further vesicle fusion.

Accidental oral intake (eating of poisoned food) with clostridial BoNT usually led to generalized flaccid paresis of all voluntary muscles within hours and causes severe respiratory failure that usually led to respirator ventilation and intensive care unit therapy for 3 month (Botulism). On the opposite therapeutic intramuscular injection of defined amounts of BoNT-A or -B (products available, doses are calculated in so called Mouse Units = MU) led to a dose dependent paresis (blockade of muscle contraction) of the muscles injected. BoNT-A blocks Achetylcholin release at the motor endplates and therefore stops voluntary and involuntary muscle contraction follow intramuscular injection of the drugs available. Only the BoNT-A products are licensed to be used in focal spasticity treatment [42]. To be sure to inject BoNT A in

the muscles intended, e.g. in small and deep seated muscles, injection guidance techniques (ultrasound-, electrical stimulation- or electromyographic-guidance methods) should be used to inject the toxin diluted in normal saline accurately [50].

A single spastic muscle is rarely treated solely and it is important that the individual spastic pattern of muscle under- and over-activity, at rest and while moving, is correctly understood by the evaluating therapists and injection physicians, so that all relevant muscles can be treated appropriately. To optimize the uptake rate of BoNT-A the injected muscles should be activated following injection e.g. by electrical stimulation or by inducing spasticity with e.g. stretching of the spastic muscles to enhance SV2-receptor exposure and therefore the binding and consecutive uptake of the BoNT injected [19].

Beside blocking voluntary and involuntary muscle activity BoNT injections also induces changes in afferent input to spinal sensomotor networks via denervation of the intra-fusal muscle fibres and therefore reduces changes in afferent IA input. In addition, BoNT-A injections into the shorter of the co-contracting antagonistic muscles in spastic dystonia around the joint will augment stretching activities and allow to actively train antagonistic coordination.

Following injection of an adequate dose of BoNT-A into a spastic muscle it requires 24–72 h to detect reduction in muscle force. The peak effect on force occurs within 10 days to 4 weeks. Clinical improvements in SMD can be expected from BoNT-A injections for up to 12–24 weeks [40].

Clinical experience and published studies with the different BoNT-A drugs has shown that all products licensed for spasticity treatment are well tolerated and associated with few adverse events across all regions injected for spasticity treatment [40]. Local adverse effects (AE) are caused by local diffusion of BoNT-A from the target muscle into adjacent muscles or tissues. Systemic AE occur in tissues distant from the injection site and based upon BoNT-A transport within the lymphatic or blood circulation. AE of the different drugs occur in a typical latency about one week after injection of the toxin. Severity and duration of local and systemic AE depend on the local or total dose of the different products applied. Therefore concerning latency of AE all BoNT-A drugs have similar AE profiles. Neutralising antibodies seems to be no longer a problem in spasticity treatment for incobotulinumtoxinA and onabotulinumtoxinA. With more than a million injections of incobotulinumtoxinA never ever secondary non-response due to neutralising antibodies was proofen and with the reformulation of onabotulinumtoxin A in 1997 the rate of antibodies in onabotulinumtoxinA treated patients was calculated below a rate of 1%. The incidence of neutralising antibodies following repetitive abobotulinumtoxin A injections is calculated from published studies with 3–5%.

It is evident from controlled studies that in order to induce an optimal uptake of the toxin following injection within muscles with diffuse endplate distribution injected volume per muscle should be distributed in more injection sites and this is particularly important in larger muscles, whereas in muscles with endplate bands the dose of toxin should be divided across this defined endplate region at one or two sites.

It must be recognised and included in the sequence of the management plan in spasticity that BoNT-A treatment effects are temporary. With respect to

combination of different treatment approaches it could be used to opening a so called "window of opportunity" or "therapeutic window" with less spastic muscle tone and allow for a better combination of neurorehabilitative treatment approaches by reducing muscle tone increase with BoNT-A and allow to better re-establish antagonistic coordination. Reversibility of BoNT-A effects may lead to repeated treatment in post-acute and chronic spastic paresis with muscle tone increase, muscle overactivity, spastic dystonia and disturbed reciprocal inhibition, but may perhaps modify the course of muscle overactivity in early post-stroke intervention. Nowadays we know from controlled studies in the post-acute phase of stroke rehabilitation (less than 3 month following stroke) that BoNT-A injected before spasticity become chronic doses injected can be lower and improvements on impairment and passive function level tend to be more pronounced and longer lasting [36].

Several studies have investigated the effect of BoNT-A on post-stroke upper limb function and mobility, usually combined with an exercise programmes and adjunctive treatments. Treatment with BoNT-A gave a notable improvement in hand function, and hence improvements in self-care tasks and other activities of daily living, and alleviated pain [29]. Reaching and grasping functions were improved in individuals but not significantly in the verum groups in most controlled trials. The optimal time to administer BoNT-A may be when muscle overactivity becomes evident and bothersome to the rehabilitation program of the individual patient, resulting in impairment of active and passive functions, hinders active training programs or robot based training and therefore increased disability and associated reactions, or when it induces pain [35].

As mentioned above early single-dose BoNT-A treatments (<3 months after stroke) of spasticity has been investigated in three upper limb [6, 20, 35] and in one in the lower limb studies [10]. Main result of this studies was compared with placebo a significant and sustained reduction in muscle tone observed for 6 months following a single fixed dose of BoNT-A. Early use of BoNT-A therefore may extend the time window for motor re-learning with active motor traing by decreasing overactive of extrafusal muscle fibres (spasticity) and afferences from intrafusal muscle fibres to spinal sensomotor networks through chemodenervation of extra and intrafusal muscle fibres. With this the early BoNT-A intervention paradigm may potentially modify the natural progress of spasticity, may prevent spasticity and spastic dystonia-related complications in SMD.

BoNT-A drugs available are different and not interchangeable. The most important difference in BoNT drugs available refers to the serotype used. So far, only BoNT-A and BoNT-B are commercially available, whereas BoNT-C and BoNT-F have been tried in humans in studies in dystonia only.

The currently available BoNT-A drugs in Europe and North America are: Botox® (onabotulinumtoxin A; Allergan Inc, Irvine, CA, USA), Dysport® (abobotulinumtoxin A; Ipsen Ltd, Slough, Berks, UK), Xeomin® (incobotulinumtoxin A; Merz Pharmaceuticals, Frankfurt/M, Germany).

Neurobloc® (rimabotulinumtoxin B; Eisai Europe Limited, London, UK) is the only type B drug that is available in Europe. In the US and in some other countries

NeuroBloc® is distributed as Myobloc® (rimabotulinumtoxin B; Solstice Neurosciences Inc, Malvern, PA, USA).

Botox® was the first BoNT drug to be registered in 1989, whereas Dysport® was registered in 1991, Hengli® in 1993, NeuroBloc®/Myobloc® in 2000 and Xeomin® in 2005. For all BoNT-A drugs instead incobotulinumtoxinA special storage temperatures are required. Xeomin® is the only drug which can be stored at room temperature. Additional BoNT drugs are the Chinese Hengli® (Lanzhou Institute of Biological Products, Lanzhou, Gansu Province, China) which is based upon BoNT type A. It is distributed in some Asian and South American countries (e.g. Brazil) as Prosigne®. Neuronox® (Medy-Tox, Ochang, South Korea) is another BoNT-A drug available in South Korea and in some other Asian countries too.

Dosages of the BoNT-A drugs that are licensed in European countries and North America for the treatment of spasticity are given in the Summary of Product Characteristics (SPC) of each drug, however the doses and muscles licensed in the different countries of each drug vary in between different countries.

Apart from that it is important that dosing should be determined by the individual patient's condition (e.g. body weight, muscle mass, sever of spasticity) and the goals of treatment and can be reassessed according to the response to treatment. It is common clinical practice to initiate BoNT type A therapy at low, but effective, doses and titrate upwards as effects become evident. Therapeutic dosages of BoNT-A drugs in spasticity vary more widely than with almost any other drug. Whereas minimum therapeutic BoNT A doses used for intrinsic hand muscles as low as 10–15 MU inco-or onabotulinumtoxin A, maximum reported BoNT A doses used for severe spasticity with involvement of upper and lower limbs can reach 1500 MU abobotulinumtoxinA [16], 600 MU onabotulinumtoxinA [50] or 800 MU incobotulinumtoxin A [53]. When incobotulinumtoxinA are used in high doses per injection session (up to 800 MU) in a setting including adequate dosing per muscle (according the published we move recommendations) and injection site (not more than 50 MU onabotulinumtoxinA and incobotulinumtoxinA per site) and inclusion of injection guidance for deep seated or small muscles (muscle ultrasound or electrical stimulation injection guidance) local and systemic motor and autonomic adverse effects are reported very rarely [53]. Same is true when using abobotulinumtoxin A in doses of 1500 MU [16].

4.11 Management of Severe Multisegmental and Generalized Spasticity and Spastic Contractures

Oral antispastic drugs are licensed for systemic treatment of spasticity, most drugs available without any restriction on distribution of spasticity or etiology of spasticity (exclusion for Tolperison and Sativex: Tolperison is licensed for PSS only and Sativex for pain and spasticity in MS only) [26, 31]. Still these oral antispastic

drugs are used widely. Specially baclofen (Gamma-Aminoacid-[GABA-] B-Agonist) and tizanidin (central Alpha2-Agonist) are well known by GPs and non-neurologists and are given widely without specific goals when clinical signs of spasticity appear. Other antispastic oral drugs are also in use like Benzodiazepines (GABA-A-Agonisten) and Dantrolen (pheripheral acting muscle relaxans that inhibit Ca-Ions at the level oft he muscle), tolperison (central acting inhibitor of Na-influx at neurons, licensed in Germany only in stroke spasticity) and gabapentine.

Sativex is the only oromucosal spray available to treat spasticity and painful spasms consisting of 2 Cannabis-components: tetrahydrocannabinol (THC) and cannabidiol (CBD, licenced for pain, spasms and spasticity management in MS) [26].

Central acting drugs directed against positive symptoms of UMNS (e.g. muscle tone increase, spastic dystonia, spasms, and spasticity) are introducing inhibition in cortical level or spinal interneuron pool and therefore not only inhibit the different features of the UMNS but also block voluntary muscle activity and core muscle tone, as well as cognitive activity and vigilance. Dantrole as well is not a selective inhibitor of spastic muscle tone and it acts directly in the muscle and is known to be hepatotoxic. Beside this negative impact of oral antispastics on voluntary muscle force (and core stability and breathing volume) all central acting oral agents are known to frequently cause side effects like sedation, vertigo, dry mouth and cognitive impairment and therefore are not recommended to be introduced as first line treatment in focal, segmental and multi-segmental cerebral spasticity [26, 49].

As well in a controlled "head to head" comparison Simpson et al. [41] where able to show that patients with post-stroke spasticity profit much more (antispastic effect much better in size and less side effects) from focal treatment with BoNT A with respect to their focal and segmental spasticity than from systemic oral treatment with Tizanidin [41]. On the contrary many specialists in spinal cord rehabilitation recommend to first line—start with orals in spinal spasticity before moving to other spasticity management regimes.

The first line recommendation of intrathecal baclofen (ITB) management in severe multisegmental and generalized forms of spasticity from SCI, TBI, MS and CP is based on well designed studies that showed significant improvement in positive signs of UMNS and no weakening on residual muscle force in non-affected body segments when dose of ITB is titrated upward and programming mode of the implanted pump is used in managing individual spasticity of the patients implanted with a pump. As the pump for ITB has to be implanted and many components of the implanted system has to function smooth side effect frequency compared to conventional treatment with oral drugs is higher in ITB spasticity management. Therefore following concent of patient and/or caregiver it is recommended to use this concept in severe segmental and generalized forms of UMNS and to combine treatment as recommended with physical measures and if necessary additional focal treatment with BoNT-A [26].

If spasticity is accompanied by neuropathic pain syndroms (e.g. as often the case in thalamic stroke, TBI or SCI) it is recommended to add to antispastic local management with BoNT-A in the beginning antineuropathic—analgesic drugs like GABA-analoga Gabapentin or Pregabalin (central Na-blocker, licensed as

antiepileptic and anxiolytic drug) and pain modulators (antidepressive agents). If indicated also oromucosal spray of THC and CBD (Sativex) or other cannabis derivates (THC and THC/CBD oil) or canaboids (Nabilone) are effective symptomatic drugs in treating combinations of severe pain and severe spasticity [26, 52].

In case of no response to antispasticity management and major impairment and activity limitations from spastic contractures plastic-orthopedic surgical procedure like fasciotomia, tendon lengthening or complex tendon-muscle-bony-surgery should be discussed to gain improved activity and pain levels. As well reconstructive surgery with tendon or muscle transfers is an option to reach mobility and dexterity goals and overcome activity and participation limitations from severe spastic paresis [8, 50].

References

1. Ada L, Vattanasilp W, O'Dwyer NJ, et al. Does spasticity contribute to walking dysfunction after stroke? J Neurol Neurosurg Psychiatry. 1998;64(5):628–35.
2. Ansari NN, Naghdi S, Arab TK, Jalaie S. The interrater and intrarater reliability of the modified Ashworth scale in the assessment of muscle spasticity: limb and muscle group effect. NeuroRehabilitation. 2008;23(3):231–7.
3. Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. Practitioner. 1964;192:540–2.
4. Burke D, Wissel J, Donnan GA. Pathophysiology of spasticity in stroke, *Neurology*, 2013; 80(3)(suppl 2):S20–6.
5. Caty GD, Detrembleur C, Bleyenheuft C, et al. Effect of simultaneous botulinum toxin injections into several muscles on impairment, activity, participation, and quality of life among stroke patients presenting with a stiff knee gait. Stroke. 2008;39(10):2803–8.
6. Cousins E, Ward A, Roffe C, et al. 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. Clin Rehabil. 2010;24:501–13.
7. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. Lancet Neurol. 2007;6:725–33.
8. Esquenazi A, Novak I, Sheean G, et al. International consensus statement for the use of botulinum toxin treatment in adults and children with neurological impairments–introduction. Eur J Neurol. 2010;17(Suppl 2):1–8.
9. Flash T, Hogan N. The coordination of arm movements: an experimentally confirmed mathematical model. J Neurosci. 1985;5(7):1688–703.
10. Fietzek UM, Kossmehl P, Schelosky L, et al. Early botulinum toxin treatment for spastic pes equinovarus—a randomized double-blind placebo-controlled study. Eur J Neurol. 2014;21 (8):1089–95.
11. Foley N, Pereira S, Salter K, et al. Treatment with botulinum toxin improves upper-extremity function post stroke: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2013;94:977–89.
12. Gracies JM. Pathophysiology of impairment in patients with spasticity and use of stretch as a treatment of spastic hypertonia. Physical Med Rehabil Clin N Am. 2001;12:747–68.
13. Gracies JM. Pathophysiology of spastic paresis. I: paresis and soft tissue changes. Muscle Nerve. 2005;31(5):535–51.
14. Gracies JM. Pathophysiology of spastic paresis. II: emergence of muscle overactivity. Muscle Nerve. 2005;31(5):552–71.

15. Gracies J-M. Coefficients of impairment in deforming spastic paresis. Ann Phys Rehabil Med. 2015;58(3):173–8.
16. Gracies JM, Brashear A, Jech R, et al. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomized controlled trail. Lancet Neurol. 2015;14:992–1001.
17. Haugh AB, Pandyan AD. Johnson GR A systematic review of the Tardieu Scale for the measurement of spasticity. Disabil Research. 2006;28(15):899–907.
18. Hefter H, Jost WH, Reißig A, et al. Classification of posture in poststroke upper limb spasticity: a potential decision tool for botulinum toxin A treatment. Int J Rehabil Res. 2012;35:227–33.
19. Hesse S. Recovery of gait and other motor functions after stroke. Restaurative Neurol Neurosci. 22(2004):359–69.
20. Hesse S, Mach H, Fröhlich S, et al. An early botulinum toxin A treatment in subacute stroke patients may prevent a disabling finger flexor stiffness six months later: a randomized controlled trial. Clin Rehabil. 2012;26:237–45.
21. Kwah LK, Harvey LA, Diong JH, et al. Half of the adults who present to hospital with stroke develop at least one contracture within six months: an observational study. J Physiother. 2012;58(1):41–7.
22. Lance JW. Pathophysiology of spasticity and clinical experience with baclofen. 185–220. In: Feldman R, Young R, Koella W, editors. Spasticity: disordered motor control. Chicago: Yearbook Medical Publishers; 1980. p. 185–220.
23. Lance JW. The control of muscle tone, reflexes, and movement: Robert Wartenberg lecture. Neurology. 1980;30(12):1303–13.
24. Lee KW, Kim SB, Lee JH, et al. Effect of upper extremity Robot-assisted exercise on spasticity in stroke patients. Ann Rehabil Med. 2016;40(6):961–71.
25. Lieber RL, Steinman S, Barash IA, et al. Structural and functional changes in spastic skeletal muscle. Muscle Nerve. 2004;29(5):615–27.
26. Liepert J. Therapie des spastischen Syndroms. Aus: Hans-Christoph Diener, Christian Weimar (Hrsg.) Leitlinien für Diagnostik und Therapie in der Neurologie. Herausgegeben von der Kommission "Leitlinien" der Deutschen Gesellschaft für Neurologie. Thieme Verlag, Stuttgart; 2012.
27. Malhotra S, Pandyan AD, Day CR, et al. Spasticity, an impairment that is poorly defined and poorly measured. Clin Rehabil. 2009;23(7):651–8.
28. Mayer NH. Clinicophysiologic concepts of spasticity and motor dysfunction in adults with upper motoneuron lesion. Muscle Nerv. 1997;20(suppl 6):S1–13.
29. Mills PB, Finlayson H, Sudol M, et al. Systematic review of adjunct therapies to improve outcomes following botulinum toxin injection for treatment of limb spasticity. Clinical Rehabil. 2016; 0269215515593783.
30. Olsson MC, Krüger M, Meyer L-H, et al. Fibre type-specific increase in passive muscle tension in spinal cord-injured subjects with spasticity. J Physiol. 2006;577(Pt 1):339–52.
31. Olvey EL, Armstrong EP, Grizzle AJ. Contemporary pharmacologic treatments for spasticity of the upper limb after stroke: a systematic review. Clin Ther. 2010;32:2282–303.
32. Pandyan AD, Gregoric M, Barnes MP, et al. Spasticity: clinical perceptions, neurological realities and meaningful measurement. Disabil Rehabil. 2005;27:2–6.
33. Platz T, Eickhof C, Nuyens G, Vuadens P. Clinical scales for the assessment of spasticity, associated phenomena, and function: a systematic review of the literature. Disabil Rehabil. 2005;27:7–18.
34. Platz T, Vuadeus P, Eickhof C, et al. REPAS, a summary rating scale for resistance to passive movement: item selection, reliability and validity. Disabil Rehabil. 2008;30(1):44–53.
35. Rosales R, Botulinum toxin therapy as an early intervention for post-stroke spasticity: beyond a functional viewpoint. J Neurol Sciences. 2017; 382:187–8.
36. Rosales RL, Kong KH, Goh KJ, et al. Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke: a randomized controlled trial. Neurorehabil Neural Repair. 2012;26:812–21.

37. Sheean G. The pathophysiology of spasticity, Eur J Neurol. 2002;9(s1)(suppl 1):3–9, 53–61.
38. Sheean G. Botulinum toxin treatment of adult spasticity. Expert Rev Neurotherapeutics. 2003;3, 773–85.
39. Sherwood AM, Mc Kay WB, Dimitrijevic MR. Motor control after spinal cord injury: assessment using surface EMG. Muscle Nerve. 1996;19(8):966–79.
40. Simpson DM, Gracies JM, Graham HK, et al. Assessment: Botulinum neurotoxin for the treatment of spasticity (an evidence-based review): report of the therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008;70:1691–8.
41. Simpson DM, Gracies JM, Yablon SA, et al. BoNT/TZD Study Team: Botulinum neurotoxin versus tizanidine in upper limb spasticity: a placebo-controlled study. J Neurol Neurosurg Psychiatry. 2009;80:380–5.
42. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016;86(19):1818–26.
43. Thilmann AF, Fellows SJ, Gams E. The mechanism of spastic muscle tone. Variation in reflex gain over the time course of spasticity. Brain. 1991;14:233–44.
44. Turner-Stokes L, Ward A. Botulinum toxin in the management of spasticity in adults. Clin Med. 2002;2:128–30.
45. Turner-Stokes L. Goal attainment scaling (GAS) in rehabilitation: a practical guide. Clin Rehabil. 2009;23:362–70.
46. Turner-Stokes L, Williams H, Johnson J. Goal attainment scaling: does it provide added value as a person-centred measure for evaluation of outcome in neurorehabilitation following acquired brain injury? J Rehabil Med. 2009;41:528–35.
47. Vinti M, Couillandre A, Hausselle J, et al. Influence of effort intensity and gastrocnemius stretch on co-contraction and torque production in the healthy and paretic ankle. Clin Neurophysiol. 2013;124(3):528–35.
48. Ward AB, Wissel J, Borg J, et al. Functional goal achievement in post-stroke spasticity patients: the BOTOX(R) Economic Spasticity Trial (BEST). J Rehabil Med. 2014;46:504–13.
49. Winter T, Wissel J. Behandlung der Spastizität nach Schlaganfall. Konsultationsfassung der DGNR-Leitlinie. Neurologie und Rehabilitation. 2013;19:285–309.
50. Wissel J, Ward AB, Erztgaard P, et al. European consensus table on the use of botulinum toxin type A in adult spasticity. J Rehabil Med. 2009;41:13–25.
51. Wissel J, Manack A, Brainin M. Toward an epidemiology of poststroke spasticity. Neurology. 2013;80(Suppl 2):S13–9.
52. Wissel J, Ganapathy V, Ward AB, et al. OnabotulinumtoxinA improves pain in patients with post-stroke spasticity: findings from a randomized, double-blind. Placebo-controlled Trial. J Pain Sympt Manag. 2016;52(1):17–26.
53. Wissel J, Djamel Bensmail D, Ferreira JJ et al. Safety and efficacy of IncobotulinumtoxinA doses up to 800 U in limb spasticity: the TOWER study. Neurology. 2017.
54. Yanagisawa N, Shindo M, Morita H. Spinal mechanisms of spasticity. Electroencephalogr Clin Neurophysiol Suppl. 1999;50:190–4.
55. Zorowitz RD, Gillard PJ, Brainin M. Poststroke spasticity: sequelae and burden on stroke survivors and caregivers, Neurology, 2013;80(3)(suppl 2):S45–52.