REVIEW

Spasticity after stroke: Physiology, assessment and treatment

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Abstract

Background: Spasticity following a stroke occurs in about 30% of patients. The mechanisms underlying this disorder, however, are not well understood.
Method: This review aims to define spasticity, describe hypotheses explaining its development after a stroke, give an overview of related neuroimaging studies as well as a description of the most common scales used to quantify the degree of spasticity and finally explore which treatments are currently being used to treat this disorder.
Results: The lack of consensus is highlighted on the basis of spasticity and the associated absence of guidelines for treatment, use of drugs and rehabilitation programmes.
Conclusions: Future studies require controlled protocols to determine the efficiency of pharmacological and non-pharmacological treatments for spasticity. Neuroimaging may help predict the occurrence of spasticity and could provide insight into its neurological basis.

Introduction

Spasticity was first described by Lance [1] in 1980 as 'a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome' (p 485). This description characterizes spasticity during passive movement, but does not take into account its effects on voluntary gestures. In 1994, Young [2] added neurophysiological elements to define spasticity independently of the type of movement: 'a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes that results from abnormal intra-spinal processing of primary afferent input' (p S12). There is, however, still no consensus for the definition of spasticity and this reflects the complexity and the diversity of the phenomena. This is especially true for post-stroke motor disorders, which can give rise to a considerable variety of symptoms (e.g. clonus, dystonia, muscle weakness, abnormal reflex responses). Spasticity results from impaired reflex function and also induces changes in rheological muscle properties like stiffness, fibrosis and atrophy [3]. The 'upper motor neuron syndrome' can be defined by positive and negative signs [2]. Spasticity is part of the positive signs among other motor symptoms which occur after lesions in the descending corticospinal system such as spastic dystonia (muscle constriction in the absence of any voluntary movement), spastic co-contraction (contraction of both the agonist and antagonist muscles resulting from an abnormal pattern of commands in the descending supraspinal pathway), extensor or flexor spasms, clonus, exaggerated deep tendon reflexes and associated reaction [4, 5]. On the other hand, negative signs are muscle weakness, loss of dexterity and fatigue (Table I).

This disorder is a common symptom after stroke, arising in about 30% of patients, and usually occurs within the first few days or weeks [6]. However, the onset of spasticity is highly variable and can occur in the short-, medium- or long-term post-stroke period [7]. A study by Wissel et al. [8] showed that 25% of patients with stroke suffer from spasticity within the first 6 weeks of the event. They also observed that spasticity primarily affects the elbow (79% of patients), the wrist (66%) and the ankle (66%) [8]. In the upper limbs, the most frequent pattern of arm spasticity is internal rotation and adduction of the shoulder coupled with flexion at the elbow, the wrist and the fingers [9, 10]. In the lower limbs, adduction and extension of the knee with equinovarus foot is the most observed pattern (Figure 1).

A recent study showed that the prevalence of spasticity does not differ between the upper and the lower limbs. Severe spasticity (Modified Ashworth Scale; MAS ≥3), though, was observed more frequently in the upper limb muscles [11]. Nevertheless, major spasticity is relatively rare. A high degree of paresis and hypoesthesia at stroke onset has been suggested as one of the predictors for the development of spasticity [11, 12]. Other risk factors were also identified for the development of permanent spasticity after a stroke: (i) any paresis in affected limb, (ii) more severe paresis at 16 weeks compared to the first week, (iii) MAS ≥2 in at least one joint within 6 weeks after stroke, (iv) more than

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Table I. Description of positive and negative signs observed in cases of upper motor neuron syndrome due to stroke [18].

Positive signs	
Increased tendon reflexes	Result from hyperexcitability of the stretch reflex
Clonus	Series of involuntary, rhythmic, muscular contractions and relaxations due to a self re-excitation of hyperactive stretch reflexes in the affected muscle
Positive Babinski sign	Extension of the big toe, while the other toes fan outwardly in response to rubbing of the sole of the foot. It indicates a lesion of the corticospinal tract
Spasticity	Muscle hypertonia during movement (active or passive), dependent upon velocity of muscle stretch
Extensor/flexor spasms	Spasms occur spontaneously or in response to stimulation (movement of the leg, change of position). The most common pattern of flexor spasm is flexion of the hip, knee and ankle
Spastic co-contraction (during movement)	Agonist and antagonist muscles co-contract simultaneously inappropriately and thus disrupt normal limb movement. This is due to the perturbation of the spinal reflexes that contribute to reciprocal innervation
Associated reactions and other dyssynergic stereotypical spastic dystonia	Remote form of synkinesis due to a failure to inhibit spread of motor activity (e.g. flexion of the elbow simultaneously to flexion of the hip during walking)
Negative signs	
Muscle weakness	Muscles have lower strength due to the loss of corticospinal drive
Loss of dexterity	Loss of hand precise movements, such as opposition of the thumb due to a weakness of the intrinsic and extrinsic hand muscles
Fatigability	Greater effort required to perform a movement leading to tiredness

Figure 1. Left: equinovarus feet; right: upper limbs with a spastic pattern in adduction and internal rotation of the shoulder and flexion of the elbow, wrist and fingers.

two joints affected by increased muscle tone, (v) hemispasticity within 6 weeks after stroke and (vi) lower Barthel Index [8].

Spastic symptoms can induce pain, ankylosis, tendon retraction or muscle weakness in patients, which may limit the potential success of rehabilitation [13, 14]. Spasticity can also affect quality-of-life and be highly detrimental to daily function [15]. There is currently a lack of specific guidelines for the stratification and individualization of rehabilitation programmes. First, variables that can reliably predict recovery have to be identified. Second, the pathophysiology of motor disorder following stroke must be explored in order to improve rehabilitation and clarify outcomes.

This review will explore the different hypotheses that attempt to explain the development of spasticity following cortical damage caused by a stroke. This may help to describe the mechanisms underlying the syndrome. A brief overview will then be given of neuroimaging studies of motor disorders following stroke and commonly used scales for quantifying the degree of spasticity. Finally, the most prominent existing treatments and revalidation programmes will be identified and discussed.

Physiopathology

Spasticity is induced by the dissociation or disintegration of motor responses from sensory input, leading to hyperexcitability of the segmental central nervous system (CNS) [6]. It correlates with the intensity of the sensory input (e.g., degree of stretching) and may be dependent on the CNS lesion's location [16, 17]. When the balance between inhibitory and excitatory fibres is disturbed, it can result in various aspects of upper limb syndrome, such as hypotonia, dyskinesia or spasticity. Three lesion sites have been suggested to induce spasticity: the brainstem, the cerebral cortex (in primary, secondary and supplementary motor area; SMA) and the spinal cord (pyramidal tract) [18]. Following a stroke only the cortex or, in rare cases, the brainstem, are initially injured and these lesions will often induce spasticity, hyperreflexia and occasionally clonus. The onset of spasticity could be explained by an anarchic neuronal reorganization after brain lesion [14, 17, 19]. The result of this pathological neuronal reorganization may be increased activity in the muscles and exaggerated reflex responses to peripheral stimulation [16]. This hyperactivity could be related to (i) the disinhibition of the normal reflex activities

(deep tendon reflexes and flexor withdrawal reflexes), (ii) the release of primitive reflexes (e.g., Babinski sign) and (iii) active tonic stretch reflex [16, 20]. Marque et al. [21] showed that a potent excitation of heteronymous group II (fast twitch muscle) quadriceps motor neurons could contribute to spasticity in hemiplegic patients. They observed a facilitation of the H reflex—a muscle reflex appearing after electrical stimulation of sensory fibres—on the spastic side of the quadriceps, when compared to the unaffected side and to a healthy control population. An improvement of the transmission in the inter-neuronal pathway co-activated by the two groups, I (low oxidative) and II (fast twitch), may result from a change in their descending control pathway in spastic hemiplegic patients. These results support the hypothesis that hyperactivity of the spinal reflex induces spasticity.

For intentional movements, central voluntary motor command may be disturbed at various levels and can be grouped into higher, middle and lower levels of control (Figure 2). The higher level can be sub-divided into two functional entities. The first provides the spatial and temporal representation for guidance of the movement, called 'motor imagination' or 'mental representation', whereas the second is the voluntary drive or motivation to move [22–26]. A stroke in brain areas involved in motility will lead to the activation of lower motor neurons that permit movement, despite a disturbance of the primary execution pathways, by adapting themselves to the pathological situation. One of these adaptations is increased task-related activation in regions not normally recruited for direct movement execution (i.e., SMA cingulate motor areas (CMA), premotor cortex, posterior and inferior parietal cortex, and cerebellum) [27]. These cortical modulations may play a role in the onset and development of spasticity.

As mentioned earlier, the abnormal patterns of motor unit recruitment can be explained by the failure of central voluntary activation [28, 29]. This is associated with a loss of functional units in the spinal cord as well as a significant reduction of the discharge rate in voluntarily driven motor units within the paretic muscles [30, 31]. Moreover, the alteration of motor neuron recruitment may also be related to direct changes in the properties of spinal motor neurons. Regardless of the respective contributions of supraspinal and spinal mechanisms, loss of normal motor units and firing rate reductions may decrease the efficiency of muscle contraction. This phenomenon could lead to increased effort, fatigue and weakness in voluntary force generation [32]. In addition to the neuronal disturbance, limb immobilization and disuse leads to muscle atrophy, which involves loss of normal weight-bearing, sarcomeres, skeletal muscle mass and a reduction in bone mineralization [33, 34] with accumulation of connective tissue and fat [35–38]. These phenomena further exacerbate the disabilities and side-effects induced by spasticity.

Assessment of spasticity

Behavioural evaluation

It is important to focus on three issues relating to the functional problem when evaluating spasticity: identifying the clinical pattern of motor dysfunction and its source, identifying the patient's ability to control muscles involved in the clinical pattern and differentiating the role of muscle stiffness and contracture [39].

Several scales have been developed and validated to assess spasticity in patients with brain injury. The two most
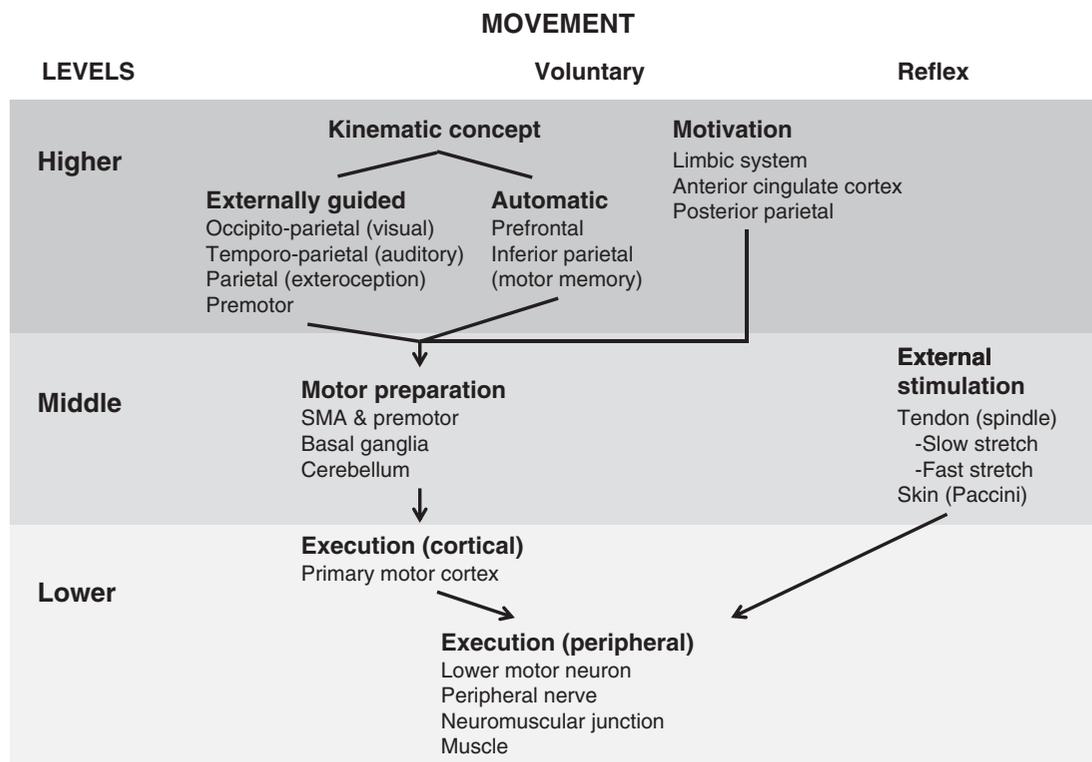

Figure 2. Categorization of voluntary and reflexive movement commands in spasticity. Focused abnormalities in the middle and the lower levels of command would alter spinal reflexes and local abnormalities in the lower level of motor command would cause significant paresis. SMA = supplementary motor area. Adapted from [125].

commonly used are the Modified Ashworth Scale [40] and the Modified Tardieu Scale [41, 42]. These scales assess the degree and angle of muscle contraction and, in the case of retraction, the amplitude of the permitted movement.

Modified Ashworth Scale (MAS)

The Modified Ashworth Scale measures the level of resistance to passive movement, but does not evaluate the velocity of passive joint movement, the angle of contraction outbreak or potential tendon retraction [43] (Table II). The MAS is effective in clinical practice because of its ease and speed of use. Moreover, this scale is widely used in research and has been highly investigated in many studies (e.g., to objectify the effect of a treatment) [5, 44–46]. Unfortunately, validation studies showed only 'moderate' to 'good' intra-rater reliability and 'poor' to 'moderate' inter-rater reliability [45, 47, 48]. Even if this scale seems to measure the resistance adequately, the reduced range of joint motion due to contractures might also limit its reliability [49]. Furthermore, it is not velocity-dependent, as Lance's definition of spasticity specified. Nevertheless, it is now established that the MAS evaluates a combination of soft tissue contracture and spastic dystonia, in addition to spasticity itself [50, 51].

Modified Tardieu Scale

In comparison with the Modified Ashworth Scale, the Modified Tardieu Scale does take into account the velocity of passive joint movement, the angle of contraction outbreak and the potential tendon retraction. In this scale, spasticity is assessed with three velocities (low, normal and fast) and the snap angle is reported as the angle of retraction [42, 52, 53] (Table II). Although this scale seems more accurate than the MAS, its validity still needs to be demonstrated [54]. The Modified Tardieu Scale tends to be more sensitive in the detection of post-treatment changes because it measures muscle resistance as well as the velocity of the movement that induces muscular contraction [53, 55, 56]. When comparing the two scales, the distribution of the mean scores correlates

poorly [53]. This may be explained by the fact that these two scales measure two different dimensions [53]. The Modified Tardieu Scale is closer to Lance's definition, as it assesses spasticity at three different velocities. Considering its good inter- and intra-subject reliability [45], the Modified Tardieu Scale might be a more appropriate instrument for the measurement of spasticity than the MAS. At present, publications regarding the validity and reliability of the Modified Tardieu Scale are very limited and only concern children with cerebral palsy, rather than adult patients with stroke. In theory, this scale demonstrates several advantages over the MAS, as it uses both a fast and slow speed of movement and incorporates an interval level measure (range of movement), as well as a subjective rating scale. Further studies need to be performed on a larger population to confirm the reliability and the specificity of this scale for assessing spasticity.

King's Hypertonicity Scale

The King's hypertonicity scale [57] could be a good alternative to measure spasticity and other symptoms of upper motor neuron syndrome because it assesses four areas: presence of increased tone, active range of motion, alternating movements and resistance to passive movement. Each component is evaluated separately and has a score of 1 (normal) to 5 (worst), which gives a total score ranging from 4–20 [57, 58]. Nevertheless, this scale needs to be validated in a wider population.

Tone Assessment Scale

The Tone Assessment Scale assigns a global spasticity score that integrates passive movement responses, resting posture and reactions associated with the assessment of spasticity in different muscle groups [59]. This scale overcomes some of the shortcomings of the MAS by establishing how tone disorders can affect limb function, such as movements necessary to eat or to walk. It is, however, only reliable for the section relating to response to passive movement at

Table II. The Modified Ashworth Scale [40] and the Modified Tardieu Scale [42].

Modified Ashworth Scale

0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch or by minimal resistance at the end of the range of motion (ROM) when the affected part(s) is (are) moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Modified Tardieu Scale

X: Quality of movement mobilization

0	No resistance throughout the course of the passive movement
1	Slight resistance throughout the course of passive movement, no clear catch at a precise angle
2	Clear catch at a precise angle, interrupting the passive movement, followed by release
3	Fatigable clonus with less than 10 seconds when maintaining the pressure and appearing at the precise angle
4	Unfatigable clonus with more than 10 seconds when maintaining the pressure and appearing at a precise angle
5	Joint is fixed

V: Measurements take place at three different velocities

V1	As slow as possible
V2	Speed of limb segment falling under gravity
V3	As fast as possible

Y: Angle of catching (muscle reaction)

various joints, except the ankle. This scale could be effective for assessing the prevalence of post-stroke spasticity and the relationship between muscle tone and function.

Daily functional assessment scales

Different scales are used depending on the pattern of clinical practices at the hospital or treatment centre. All these scales do not assess spasticity *per se*, but give other information about spasticity and its repercussions for pain and daily living. The Barthel Index is a widely used scale to assess activity limitations due to post-stroke motor impairment [60]. It evaluates 10 aspects of activity related to self-care and mobility. This scale also gives an indication about potential patient outcome. About 70% of patients showing a score lower than 40 will die or suffer from severe disabilities after 6 months, whereas 95% of patients with a score higher than 80 will recover [60, 61]. Other scales, such as the Patient's Disability and the Carer Burden Rating Scales, have also been proposed [45, 62] to assess the degree of disability caused by spasticity. The Patient's Disability Scale assesses a patient's ability to care for their spastic limb (dressing, hygiene, etc.) and to use it functionally (e.g. for walking) [45]. The Carer Burden Rating Scale also assesses care tasks, such as dressing and maintaining hygiene, but when a caregiver performs them [62]. With a similar approach, Brashear et al. [45] developed the Disability Assessment Scale, which assesses four domains of potential disability: hygiene, dressing, limb position and pain. Studies have shown that it has good inter- and intra-rater reliability, although its validity has not yet been determined [45].

It is important to stress that spasticity is not the only symptom that could be involved in motor impairment; the other signs of upper motoneuron syndrome also affect patients in their activities of daily life. Indeed, as said in the introduction, patients with stroke may suffer from dystonia, rigidity or co-contraction. Moreover, spasticity and the other positives signs of upper motoneuron syndrome could diminish a patient's ability to control their muscles during a specific movement. Finally, if stiffness, ankylosis and contracture arise, they could lead to functional difficulties and even induce joint range of motion limitation or joint fixation, mainly in triple flexion for the upper limbs and extension for the lower limbs. Table III summarizes the most common patterns of upper motor neuron syndrome [39].

Electrophysiological measures

Para-clinical tools complement behavioural measures by objectively quantifying spasticity in a more sensitive and reliable way. Techniques that register synaptic reflexes with electromyography (EMG) can be classified in two sub-groups: (i) EMG responses to electrical stimuli such as the Hoffmann reflex (H-reflex) and F-wave and (ii) EMG responses to mechanical stimuli such as the Tendon reflex (T-reflex) and polysynaptic responses [63]. The H-reflex allows assessing the excitability of the alpha motoneuron. The F-wave is a response of small amplitude that follows the M response (i.e., direct motor response caused by the stimulation of alpha fibres). Recording the H-reflex, F response and H/M or F/M ratios can provide quantitative information about

spasticity [64]. In patients with spasticity, the hyperexcitability of the stretch reflex is neurophysiologically characterized by an increase of the 'H max/M max' ratio. This could be due to an exaggerated facilitation of the H-reflex to voluntary muscle contraction and/or to the lack of inhibition associated with muscle relaxation [65]. The T-reflex quantifies the stretch reflex by recording muscle responses to tendon percussion. The amplitude of the response depends on the gain of the primary neuromuscular spindle nerve endings [66]. Finally, the study of Ib fibre inhibition can also be useful for detecting spasticity [67]. Altogether, these measurements are helpful for evaluating the degree of spasticity.

Gait and movement analysis

Gait laboratories facilitate how a victim of a stroke walks, adapts and compensates and can help assess the functional repercussions of spasticity. A gait laboratory has several cameras placed around the patient all linked to a computer. The patient has markers at various specific points on their body (e.g., iliac spines of the pelvis, condyles of the knee) and the computer calculates the trajectory of each marker. The spatial distribution of forces can be measured with pedobarography equipment. EMG can be added to investigate the activation timing of muscles and assess their contribution to gait (e.g., on the quadriceps). These analyses provide a complete breakdown of the gait movements and can help to highlight movement compensation and re-evaluate the patient after a rehabilitation programme.

Neuroimaging

To the authors' knowledge, only a few neuroimaging studies have been performed to assess spasticity. Some studies have investigated the effects of Botulinum Toxin A (BoNT-A) on spasticity in patients post-stroke. They have shown a decrease in activation of the posterior cingulate cortex and precuneus [68] following treatment and a decrease in activation in contralateral frontoparietal areas including inferior frontal, post-central and middle frontal gyrus, with activation limited to midline and contralateral sensorimotor cortices [69].

Other studies on motor disorders suggested that several brain areas are involved in the recovery of motility after a stroke [70]. An early study, using Positron Emission Tomography (PET), showed a correlation between the movement recovery in hemiparesis patients and increase of brain metabolism in the parieto-premotor areas [70]. These observations further implicate a role of this network in motor disorders following a brain lesion. Another PET study, performed by Struppler et al. [71], also showed that the improvement in a motor task (finger extension) was related to an increase of neural activation in this network, which is known to be functionally interconnected with motor areas involved in the control of arm and hand movements. In this study, an additional increase of the brain metabolism was also observed in the SMA and CMA [71]. Moreover, patients who recovered well (improvement in several motor and disability scales) showed changes within the motor system which occurred early and evolved into a more normal pattern of

Table III. Summary of the most common patterns observed in the upper motor neuron syndrome, the muscles involved and the most observed side-effects. Adapted from [6].

Pattern	Muscles involved	Side-effects
Adducted/internally rotated shoulder	Pectoralis major Teres major Latissimus dorsi Anterior deltoid Subscapularis	• Muscle contractures and pain • Shoulder stiffness and painful passive range of motion • Skin maceration, breakdown and malodor in the axilla • Difficulties for dressing • Limitation of the reaching-forward behaviour
Flexed elbow	Teres major Latissimus dorsi Long head of triceps Posterior deltoid	• Muscle contractures and pain • Persistent elbow flexion during sitting, standing and walking • Difficulties for transfer (no fulcrum), dressing and reaching objects • Skin maceration, breakdown and malodor in the antecubital fossa • Disfiguring appearance • Stretch injury to the ulnar nerve (at the bend of the elbow). The nerve is vulnerable to repeated trauma and can be compressed in the cubital tunnel leading to intrinsic muscle atrophy in the hand and weakness of ulnar wrist and finger flexion
Pronated forearm	Pronator teres Pronator quadratus	• Muscle contractures and pain • Difficulties to reach underhand to a target • Limitations to turn the patient's hand palm side up for fingernail trimming (important for patients with fingers that are flexed into the palm secondary to a clenched fist deformity) • Difficulties to feed (e.g., hold a spoon)
Flexed wrist	Flexor carpi radialis Flexor carpi ulnaris Palmaris longus Extensor carpi ulnaris	• Muscle contractures and pain • Compression of the median nerve at wrist with carpal tunnel syndrome and hand pain • Disfiguring appearance • Awkward hand placement during reaching and impairs positioning of objects held • Weakened grip strength
Clenched fist	Flexor digitorum sublimis and profundus	• Patients cannot perform the reach phase to grasp an object • Fingernails digging into palmar skin with pain • Nail bed infections • Pain when somebody attempts to pry fingers open to gain palmar access • Disfiguring appearance • Skin maceration, breakdown and malodour in the palm • Difficulties to wear gloves or hand splints • Limitation for grasping, manipulation and release of objects • Development of muscle, skin and joint contractures
Thumb-in-palm deformity	Flexor pollicis longus and brevis Adductor pollicis First dorsal interosseaous	• Difficulties to wear gloves or hand splints • Limitation of thumb extension and abduction that open up the web space before grasp • Difficulties to execute grasp patterns (three-jaw chuck, lateral grasp and tip pinch)
Flexed hip	Iliopsoas Rectus femoris Pectineus Adductors longus and brevis	• Interfered with positioning on a chair, sexuality and gait • Walking with a crouched gait pattern and compensatory knee flexion to maintain balance (leading to fatigability)
Adducted thigh	Adductor longus and brevis Adductor magnus Gracilis Iliopsoas Pectiveus	• Scissoring thighs interfere with perineal care, sexual intimacy, sitting, transfers, standing and walking • Difficulties with limb clearance and advancement during swing phase of gait
Stiff knee	Rectus femoris Vastus intermedius, medialis and lateralis Gluteus maximus	• Gait deviation with the knee remaining extended through the gait cycle • Functional lengthening of the leg during the gait with dragging of the toe and risk to trip and fall • Need of leg elevation support when seated • Problems for standing, climbing stairs and transfers
Flexed knee	Medial and lateral hamstrings	• Compensation of ipsilateral hip flexion during stance phase with flexed knee and contralateral hip and knee flexion (crouch gait pattern) • Muscle contraction and pain • Difficulties with transfers and wheelchair positioning • Limitation of limb advancement due to the lack of knees extension during the terminal swing (short step lengths) • When acting to the hip joint, hamstring cause the extension of the trunk leading to the deformity slide forward in the wheelchair
Equinovarus foot	Medial and lateral gastrocnemius Soleus Tibialis anterior and posterior Long toe flexor Extensor halluces longus	• Compression of the lateral border of the foot against the mattress, bed rail, footrest or floor • Skin breakdown on the fifth metatarsal head • Pain upon weight bearing over the lateral border of the foot • Difficulties to put on and wear shoes • Limitation of dorsiflexion during early and mid stance • Short contralateral steps • Deviant knee flexion during pre-swing • Occurrence of an early swing phase foot drag

activation, whereas little changes occurred in those with severe impairment or poor recovery.

Plasticity changes appeared primarily in the SMA in patients with good recovery, highlighting the importance of this area in the process of recovery and the dynamic nature of the modification observed. Studies using Magnetic Resonance Imaging (MRI) also note the crucial role of the SMA/CMA in the early phase of good motor recovery, as well as an increase in activity in the premotor cortex, the secondary somatosensory cortex contralateral to the affected hand and in the superior posterior regions of the cerebellar hemisphere bilaterally [72]. Furthermore, motor recovery has been correlated with activity in the primary motor cortex and SMA/CMA that becomes more normal over time [27]. These studies suggest that early changes in motor brain areas with efficient neuronal plasticity lead to better motor recovery, whereas spasticity seems to be a predictive factor of poor motor recovery after stroke [27, 72].

Treatment

Therapeutic interventions include physical therapy, occupational therapy, self-rehabilitation, orthoses equipment and assistive devices, pharmacological treatment, orthopaedic surgery and neurosurgery. This study describes various non-pharmacological patient rehabilitation therapies as well as the most common pharmacological treatments and surgery intervention.

Non-pharmacological treatment

Physical therapy

The basic treatment for all patients presenting spasticity is physical therapy [73, 74]. Limiting muscle contractures and reducing hyperactivity for at least a short period of time can be helpful. The aim of stretching is to improve the viscoelastic properties of the muscle-tendon unit and to increase its extensibility. Other structures can also be put under tension, such as tendons or connective, vascular, dermal or neural tissue [75, 76]. There is, however, no consensus about the optimal frequency, intensity, velocity and duration of stretching. A recent systematic review of the effectiveness of stretching to treat and prevent contracture in patients with brain injuries concluded that stretching does not induce significant changes in joint mobility, pain, spasticity or activity limitation [77]. Casting, a stretching method that immobilizes the limb in a stretch position, induces prolonged muscle stretching. This technique aims to improve muscle length, increase joint range of motion and to reduce contracture, pain and spasticity [78]. There are no guidelines yet, nor any scientific evidence that this method can reduce spasticity caused by neurological disorders [79]. Beside muscle stretching, muscle strength training is also used to recover functional motricity [80]. One of the most widely used approaches is the Progressive Resistance Strength Training, although, at this time, there is no gold standard for strengthening protocols [81].

Other physical therapies are used to decrease spasticity and improve motor function, such as Bobath technique, which is based on the reduction of spasticity and promotive postural reflexes prior to facilitating voluntary activity in paretic muscles through attention to trunk posture as well as controlled muscle stretch at the limbs [82]. Nonetheless, only a few studies showed that this technique is efficient to reduce spasticity in patients suffering from a stroke [83], and its effectiveness seems to be limited [84]. Additional therapies, like hydrotherapy, cryotherapy, thermotherapy, vibratory stimuli or neurodevelopmental inhibitory techniques and robotics, are used to relax muscles and reduce the intensity of spasticity. Future studies should also be investigated to determine their effectiveness [81].

Orthoses

Orthoses are frequently used in complement with physiotherapy sessions. Several types of orthoses (also called splints) exist but, as with physiotherapy, no practical guidelines have been defined so far. The aims of splinting are reductions in spasticity and pain, improvement of function, compensation for protective sensation and prevention of contracture and deformity [85]. The principal advantage of orthoses is the duration of their effectiveness, because they can be placed and left for several hours without the presence of a physiotherapist or nurse. Nevertheless, their efficacy is not yet proven by any double-blind studies and they have recently failed to provide any significant improvement in spasticity of the wrist flexor or range of wrist motion, when they were applied to the hand [86].

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS is another physical treatment that consists of electrical stimulations administered over the spastic region, the spinal dermatome or the peroneal nerve [74, 87]. This technique has been shown to reduce spasticity in antagonist muscles [88–90]. The effect seems to be related to the production of β-endorphins, which may decrease the excitability of motor neurons. It may also reduce nociceptive inputs, as suggested by the gate control theory, by regulating the transmission of pain impulses [91, 92]. Moreover, it has been suggested that TENS could facilitate cortical synaptic reorganization and motor output by increasing sensory input, due to the stimulation of large diameter A_β fibres. The efficiency of TENS still needs to be further investigated through randomized controlled trials. Other stimulation methods, such as ultrasound and transcranial direct current stimulation, which have, until now, only been used in research, have shown promising positive effects against spasticity [93, 94]. Further studies are still needed to determine the most efficient parameters and to understand the sustained mechanisms that underlie these stimulation methods.

Pharmacological agents

Anti-spastic treatment should be introduced when the patient suffers from motor disability due to spasticity. After a stroke, motor hyperactivity is the only motor disorder (see the pathophysiology section) that can benefit from drug treatment. Medication should be tailored according to the lesion area (e.g., cortical, spinal cord) and the intended effects. Pharmacological treatments either act on the CNS or directly

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Table IV. Dosing, mechanism of action and side-effects of pharmacological treatment of spasticity. Adapted from [98, 108, 126].

Drug	Dose	Administration	Mechanism of action	Side-effects	FDA approved
Diazepam	5–20 mg 3 times daily	Oral	Increases the affinity of GABA for the $GABA_a$ receptor complex leading to an increase in presynaptic inhibition and reduction of synaptic reflexes	Sedation, weakness, hypotension, adverse gastro-intestinal effects, memory trouble, confusion, depression and ataxia	No
Clonazepam	0.5–1.0 mg once daily (bedtime)	Oral	same as above	Weakness, hypotension, ataxia, disco-ordination, sedation, depression and memory impairment. Prolonged use could increase the risk of addiction	No
Gabapentin	240–360 mg daily	Oral	Structurally similar to the GABA; Increases the brain level of GABA	Fainting, somnolence, nystagmus, ataxia, headache, tremor	No
Baclofen	5–20 mg 3–4 times daily	Oral	Centrally acting GABA analogue; Binds to $GABA_b$ receptor at the presynaptic terminal and inhibits the muscle stretch reflex	Sedation, dizziness, weakness, fatigue, nausea. Lowers seizure threshold	Yes
Tizanidine	4–36 mg daily	Oral	Imidazole derivative, with agonist action on alpha-2 adrenergic receptors in CNS	Sedation, dizziness, mild hypotension, weakness, hepatotoxicity	Yes
Dantrolene	25–100 mg 4 times daily	Oral	Interferes with the release of calcium from the sarcoplasmic reticulum of the muscle	Generalized muscle weakness, mild sedation, dizziness, nausea, diahhrea, hepatotoxicity	Yes
Phenol/alcohol	30 mg/kg	Injectable	Chemical denervation of the muscles	Burning and dysesthesias. Damage of the sensory nerves and pain	No
Botulinum toxin	10–15 units/kg	Injectable	Inhibit the release of acetylcholine at the neuromuscular junction	Pain (during injection) Local weakness Swallowing trouble for patients with respiratory and swallowing disorders	Yes (Botox-onabotulinumtoxin A)
Intrathecal baclofen	25–1000 µg daily	Intrathecal pump	Binds to GABAb receptor at the presynaptic terminal and inhibits the muscle stretch reflex	Decreased ambulation speed and muscle weakness	Yes

on the muscles. Several treatments aim to reduce muscle tone, either through oral or injectable administrations or through an intrathecal pump. Their efficiency, however, remains controversial and not well understood (Table IV).

Oral treatments

- *Baclofen*, a gamma-Aminobutyric acid (GABA) agonist, is the most commonly administered oral treatment against spasticity. Baclofen crosses the blood–brain barrier and binds at the $GABA_b$ receptors of the spinal cord. Potential adverse effects such as sedation, fatigue and drowsiness lead to oral drugs being considered as a second treatment line in patients with stroke, especially during early rehabilitation [95–97]. Despite its widespread use in patients with severe brain injuries, its efficiency for combating spasticity still need to be widely proven [97].

- *Benzodiazepines*, such as diazepam or clonazepam, increase the affinity of GABA for the $GABA_a$ receptor complex. This leads to an increase in pre-synaptic inhibition and, therefore, a reduction of spinal reflex pathway [98]. Although they reduce muscle hypercontraction, these agents also induce muscle weakness and drowsiness [98]. Since past studies on benzodiazepines in post-stroke rehabilitation showed some detrimental effects, they are no longer recommended [99].

- *Gabapentin* is an anti-convulsant structurally similar to GABA. Although this drug is usually used to treat neuropathic pain, it has been shown to be effective for decreasing spasticity at high doses (e.g. 2400–3600 mg per day) [81, 98, 100]. Gabapentin intake seems to result in increased brain levels of GABA. However, its exact mechanism of action is not well understood. This agent has several adverse effects such as fainting, somnolence, nystagmus, ataxia, headache and tremor [98].

- *Tizanidine*, an adrenoceptor agonist, is another central-acting drug that increases the pre-synaptic inhibition of motor neurons [101, 102]. This pharmacological agent is used less often than other drugs like Baclofen, perhaps because of its novelty or potentially its side-effects (e.g., sedation, hypotension, asthenia, dizziness, hallucination or hepatotoxicity) [103, 104].
- *Dandrolene sodium* is a muscle relaxant that acts by binding the ryanodine receptor and affects calcium release, specifically in skeletal muscle to inhibit excitation/contraction coupling, thereby reducing spasticity [105]. In doses greater than 200–300 mg per day it also has a sedative effect [106].

It is important to stress that all long-term treatments will have to be revised (e.g., for therapeutic windows and dose changes). Indeed, the patient's condition can change (e.g., increased spasticity or, on the contrary, surgery or botulinum toxin injection which reduce spasticity). Moreover, the patient can also present a habituation to the treatment.

Injectable treatments

- *Phenol and alcohol* are neurolytic agents which induce chemodenervation [107]. The recommended concentration is 5–7% for phenol and 45–100% for alcohol. Unfortunately, dysesthesia and soft-tissue fibrosis can occur because these substances lack specificity [98].
- *Botulinum toxin* (BoNT) agents, administered by intramuscular injection, are also available for the treatment of localized spasticity and have been shown to increase patient's ability to actively mobilize their upper and lower limbs and improve their autonomy (e.g. self-care, walking) [108–110]. Electrostimulation is the most strongly recommended localization technique, to precisely identify the muscle that needs to be treated, BoNT-A specifically inhibits acetylcholine release at the neuromuscular junction, thus reducing muscle contractions [111]. In comparison with phenol and alcohol, BoNT-A is more selective due to the easy titration and administration [98]. The effectiveness of BoNT-A for reducing spasticity in upper limbs (elbow, wrist and fingers) as assessed by the MAS and on functional abilities (e.g., Barthel Index), was proven by several randomized double-blind placebo-controlled studies [110, 112, 113]. It also seems to be effective for decreasing spasticity in the lower limbs (foot and calf) [114]. Moreover, Simpson et al. [115] showed that BoNT-A is safer and more effective than Tizanidine, reporting a higher reduction of muscle tone in the upper limbs and lower incidence of side-effects. Aside from acting on the tonus and increasing the efficiency of physiotherapy techniques, this injection can also have an analgesic effect [116].

Only Botox (onabotulinumtoxin A) is approved by the United States' Food and Drug Administration (FDA) for the treatment of upper limb spasticity in adults at the elbow (biceps), wrist (flexor carpi ulnaris and radialis) and fingers (flexor digitorum profundus and flexor digitorum sublimis). There are three other botulinum toxins available (abobotulinumtoxinA [Dysport], incobotulinumtoxinA [Xeomin] and rimabotulinumtoxinB [Myobloc]), but none of them are currently FDA approved for this purpose.

Below one can find recommendations made by Sheean et al. [117] for the use of BoNT-A as a treatment of upper limb spasticity:

- The effects of spasticity should be described at the level of both impairment and impact on function (active and passive).
- Treatment decisions should be based on individual evaluation, including chronicity, severity and distribution of the spasticity and weakness; the presence and severity of co-morbidities, such as contracture; the availability of support; and the goals of treatment.
- Distinguish hypertonia caused by spasticity from that of soft tissue changes.
- BoNT-A treatment is appropriate for the reduction in pain and improvement in passive function in patients with upper limb spasticity, using individualized injection patterns and treatment goals established for each patient.
- Patients most likely to benefit from BoNT-A have focal or multifocal upper limb spasticity.
- BoNT-A treatment should: be viewed as adjunct to a neurorehabilitation programme, be considered in the absence of absolute contraindication, commence when the spasticity is a significant impediment to therapy or when the problem is worsening or plateaus.
- Muscle localization may be based on surface anatomy, EMG, neuromuscular electrical stimulation, ultrasound or other appropriate imaging (e.g., Computed Tomography).
- Consider the possibility of diffusion locally and systemically and the risks of needle injury to other structures.
- Care should be taken when injecting the proximal upper limb in patients with compromised swallowing.

Concerning BoNT-B, no encouraging results have been reported its efficiency for upper limbs [118] and no study on its efficiency for the lower limbs has been done yet. In conclusion, BoNT-A can be useful for reducing spasticity and have less side-effects than other injectable drugs, such as phenol and alcohol [108, 119].

Intrathecal baclofen pomp

This technique permits direct administration of GABA agonist in the spinal cord in order to inhibit spasticity while minimizing side-effects. Its efficiency has been shown in cases of spinal cord injury and multiple sclerosis, but not yet in a patient with stroke [120, 121]. It is also more often used for spasticity of the lower limbs and the trunk. Unfortunately, in patients presenting severe spasticity this treatment showed a lack of efficiency in decreasing muscle hyperactivity. Moreover, it can induce various related side-effects, such as vigilance and respiratory disorders in the case of overdosing, cerebrospinal fluid leak with headache, catheter migration, disconnection or blockage and infection [122].

Surgical treatment

Surgical treatment of spasticity is mainly used for severe spasticity or for the after-effects induced by spasticity that become functional impairments (e.g. irreductible equinus

varus foot). These surgeries involve myelotomy, tenotomy and cordectomy to decrease muscle contraction [123]. Surgical results, though, are variable and depend on the patient. Osteotomies could also correct articulation deformity. Orthopaedic surgery can be used to decrease the side-effects of spasticity, mainly by tendon adjustment, like lengthening, releasing or transferring a specific tendon. Selective dorsal rhizotomy is mainly performed for the treatment of spasticity in children with cerebral palsy [124], but it can be employed to treat spasticity of the legs that interferes with movement or positioning. The abnormal sensory nerve rootlets are identified and sectioned, while the motor nerves remain intact. These techniques are helpful in optimizing function, especially hand opening (fingers flexor tendon) and walking (triceps surea tendon), and could prevent contractures.

Conclusion

Spasticity affects more than one out of four patients after a stroke [8]. The complexity and the diversity of spasticity make the identification of its underlying mechanisms and predisposing factors difficult. Comprehension of the spasticity phenomenon is essential so that drugs and therapeutic strategies can be developed to efficiently treat causes rather than symptoms. Failures in motor neuron activation and alterations in spinal motor neurons appear to be two major components of the pathophysiology behind paresis following a brain lesion. However, motor impairment due to paresis is greatly exacerbated by the muscles, the joint contracture and the changes in muscle contractile properties caused by immobilization. In addition, chronic disuse causes an alteration of CNS function that further reduces the ability to voluntarily recruit motor units [125]. Neuroimaging studies highlight the importance of some specific brain areas (e.g., SMA, CMA and secondary somatosensory cortex) in the development of spasticity and other motor disorders. Nevertheless, these motor issues are not well understood and further neuroimaging studies, which allow for non-invasive investigation of brain dysfunction without patient discomfort, should be done to monitor the onset and development of spasticity.

In terms of treatment, physical therapy and pharmacological treatment are essential for avoiding retraction and joint fixation, but, to date, except for BoTN on the upper limb, there are no scientific guidelines for the application of different therapies in patients suffering from spasticity. Therefore, clear guidelines need to be developed regarding the revalidation of post-stroke patients with spasticity through physical therapy, pharmacological treatment and surgical intervention. To do so, double-blind randomized controlled studies on pharmacological and non-pharmacological treatments should be performed to improve insight into spasticity.

Declaration of interest

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