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Review Article

Post-stroke Spasticity: A Review of Epidemiology, Pathophysiology, and Treatments

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SUMMARY

Spasticity is a common condition in stroke survivors, and may be associated with pain and joint contracture, leading to poor quality of life and increased caregiver burden. Although the underlying mechanisms are not well-understood, it may be due to disruption of the balance of supra-spinal inhibitory and excitatory sensory inputs directed to the spinal cord, leading to a state of disinhibition of the stretch reflex. The treatment options include physical therapy, modality and pharmacological treatments, neurolysis with phenol and botulinum toxin, and surgical treatment. A successful treatment of spasticity depends on a clear comprehension of the underlying pathophysiology, natural history, and impact on patient's performances. This review focuses on the epidemiology, presumed mechanism, clinical manifestation, and recent evidences of management.

1. Introduction

Stroke is one of the leading causes of mortality and morbidity in adults in most countries.[1–3] Spasticity is a common, but not an inevitable condition, in patients with stroke. Spasticity following stroke is often associated with pain, soft tissue stiffness, and joint contracture, and may lead to abnormal limb posture, decreased quality of life, increased treatment cost, and increased caregiver burden.[4] Early detection and management of post-stroke spasticity may not only reduce these complications, but may also improve function and increase independency in patients with spasticity.

Spasticity was first described by Lance[5] in 1980 as a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone), with exaggerated tendon jerks, resulting from hyper-excitability of the neurons involved in stretch reflex, as a component of the upper motor neuron syndrome. This definition is useful in clinical practice, because the guideline "velocity-dependent increase in tonic stretch reflexes," can distinguish spasticity from other similar movement disorders such as hypertonia, rigidity, and hyperreflexia. However, this definition ignores the important aspect of sensory input in the experience of spasticity. Some studies have found that abnormal processing of sensory inputs from muscle spindles leads to excessive reflex activation of alpha-motoneurons, and increases spasticity. The new definition from the Support Program for Assembly of a Database for Spasticity Measurement (SPASM) project defines spasticity as "disordered sensory-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles".[6] This definition takes into account the contribution of viscoelastic properties of soft tissue to joint stiffness, and the roles of proprioceptive and cutaneous sensory pathways.

2. Epidemiology

Spasticity is common after stroke, with the prevalence ranging from 30% to 80% of stroke survivors. The incidence of spasticity among paretic patients has been reported to be 27% at 1 month, 28% at 3 months, 23% and 43% at 6 months, and 34% at 18 months after stroke.[7,8] There are no large studies on the natural history of spasticity and contracture development, but permanent loss of joint range has been reported to occur within 3–6 weeks after stroke.

The onset of spasticity is highly variable in the post-stroke period, and studies have showed that spasticity develops and peaks at 1–3 months after stroke. Although the neuronal components of spasticity peak at 3 months after stroke, the muscular

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components of spasticity may increase over time, thus, contributing to increased incidence of spasticity at 6 months post-stroke.

Spasticity is more often found in the flexor muscles of the upper limb (fingers, wrist, and elbow flexors) and extensor muscles of the lower limb (knee and ankle extensors). Wissel et al observed that spasticity developed most often in elbow (79%), wrist (66%), ankle (66%), and shoulder (58%).[9] Lundström et al concluded that spasticity is observed more frequently in the upper extremities than in the lower extremities, and Urban et al found a higher degree of spasticity in the upper limb muscles.[10,11] In a review article by Sunnerhagen et al.[12] A number of predictors of post-stroke spasticity were identified. Greater severity of paresis, hemi-hypesthesia, and low Barthel Index score at baseline predicted development of more severe spasticity at final follow-up. However, the link between the neuroanatomical location and the spasticity are less established. One retrospective study by Picelli et al found that lesions in the insula, the thalamus, the basal ganglia, and white matter tracts (internal capsule, corona radiata, external capsule, and superior longitudinal fasciculus) were significantly associated with severe upper limb post-stroke spasticity[13]. Another retrospective study involved 97 patients found that putamen as one of the most important structures associated with post-stroke spasticity development[14]. Recently, a prospective cohort study by Volny et al[15]. found that there is no association between any topographical or neuroanatomic brain region with post-stroke spasticity development. Further large studies are needed to investigate this issue.

3. Pathophysiology

Spasticity is one of the upper motor neuron syndromes that cause hypertonia. Any lesion or damage along the pyramidal tract or extrapyramidal fibers can cause abnormality in muscle tone. Spasticity is generated due to the local activation of muscle spindles, but the propagation and manifestation of spasticity require involvement of the central nervous system. Spasticity can be divided into two components: spasticity mediated by the neural reflex and spasticity due to muscle contracture, which is often referred to as non-reflex spasticity. Damage of the upper motor neurons disrupts communication between the brain and the spinal cord, resulting in a state of net disinhibition of the spinal reflexes[6]. During the passive stretching of the muscles of a patient, there is sensory input from muscle spindles via primary group Ia afferent fibers to the spinal cord, and alpha-motoneurons are activated, with loss of supra-spinal inhibitory control, so that excessive muscle activation occurs[16]. In addition, the spinal interneuron, Ia and Ib interneurons, and Renshaw cell, may loss of descending inhibitory or facilitation influences from central nervous system[17]. The disruption of spinal interneuron-mediated influences might reduce the inhibition of the antagonist muscle and increase the action potentials in the sensory neurons, thus lead to excessive muscle activation[18].

However, spasticity may also be explained by changes in mechanical properties of muscles and not only by neural-mediated hyperreflexia. Several studies support the involvement of peripheral tissues, such as muscle fibers and connective tissue, in spasticity[19,20]. Chronic spasticity can reduce the sarcomere number and increase the proportion of connective tissue in the muscle. The soft tissue change might cause the pulling forces to be transmitted more readily to the muscle spindles, which can increase sensory input from muscle spindles, and increase spasticity[21] (Fig. 1). Mirbagheri et al found that intrinsic muscle stiffness was increased in patients with spasticity.[22] Gracies et al. found that muscle fibrosis and the other components of muscle contracture could increase spasticity through an overactivation of spindle afferents, and thus, increase spasticity.[23]

4. Clinical presentations

Impaired movement is usually presented in stroke patients, which may be due to a combination of upper motor neuron syndromes, including spasticity, weakness, loss of coordination and dexterity, and sustained muscles contraction. Patients with spasticity exhibit impaired functions and have a poor quality of life. Abnormal postural patterns are commonly observed, which might be related to imbalance of agonist and antagonist strength, and hypertonia. As voluntary movement is restored in stroke patients initially, synergic patterns with mass contraction of muscles are noted in the upper and lower limbs. In upper limbs, the most commonly seen patterns are adduction and internal rotation in the shoulder, flexion in the elbow, wrist and fingers, and pronation in the forearm. In the lower limbs, extensor synergy is frequently observed, with adduction in the hip, extension in the hip and knee, and equinovarus foot.[24] Later, individual movements are impaired, and synergic patterns are diminished.

Spasticity is one of the independent risk factors for the development of post-stroke pain. A prospective study conducted by Wissel et al.[9] demonstrated that spasticity is often associated with pain in stroke patients. The authors reported that 72% of the patients with spasticity experienced pain, while only 1.5% of non-spastic patients exhibited pain syndrome. Spasticity is associated with 60% cases of shoulder pain, 100% cases of elbow pain, and 33% cases of wrist pain, but no obvious correlation exists between spasticity and lower limb pain. Stretching a spastic contracted muscle could lead to disruption of muscle fibers and the release of substances that excite the muscle nociceptors, leading to nociceptive pain.[25]

5. Treatments

Spasticity can be both beneficial and deleterious. The presence of post-stroke spasticity is not necessary for treatment unless it causes significant impairments and complications.[26] In fact, spasticity beneficially contributes to mobility, maintenance of posture, vascular circulation, preservation of muscle mass and bone mineral density, and prevention of venous thrombosis.[27] Conversely, spasticity can interfere with positioning, mobility, comfort, and hygiene. Impaired dexterity is observed in individuals with both spasticity and impaired voluntary muscle movement. Therefore, clinicians caring for patients with spasticity must consider all aspects of the disability before establishing a treatment plan. It should be determined whether the patient's spasticity is aiding function or not. It may be that reducing such “useful” spasticity would be counterproductive.[28] The treatment goals for disabling post-stroke spasticity are to decrease complications and care burden, and to improve posture and ADL independence.[29] Traditionally, spasticity is managed in a sequential fashion. However, most clinicians currently apply a more synergistic approach to reducing spasticity. Regardless of the approach, any anti-spasticity treatment must be tailored according to the patient.

6. Non-pharmacological treatments

The two mainstays of non-pharmacological spasticity management are the removal of noxious stimuli that can drive hypertonicity and the application of physical modalities. The first step in managing spasticity is to identify and remove any noxious stimulus that can increase the severity of spasticity, such as a decubitus ulcer, bladder distention, urolithiasis, or urinary tract infection. As

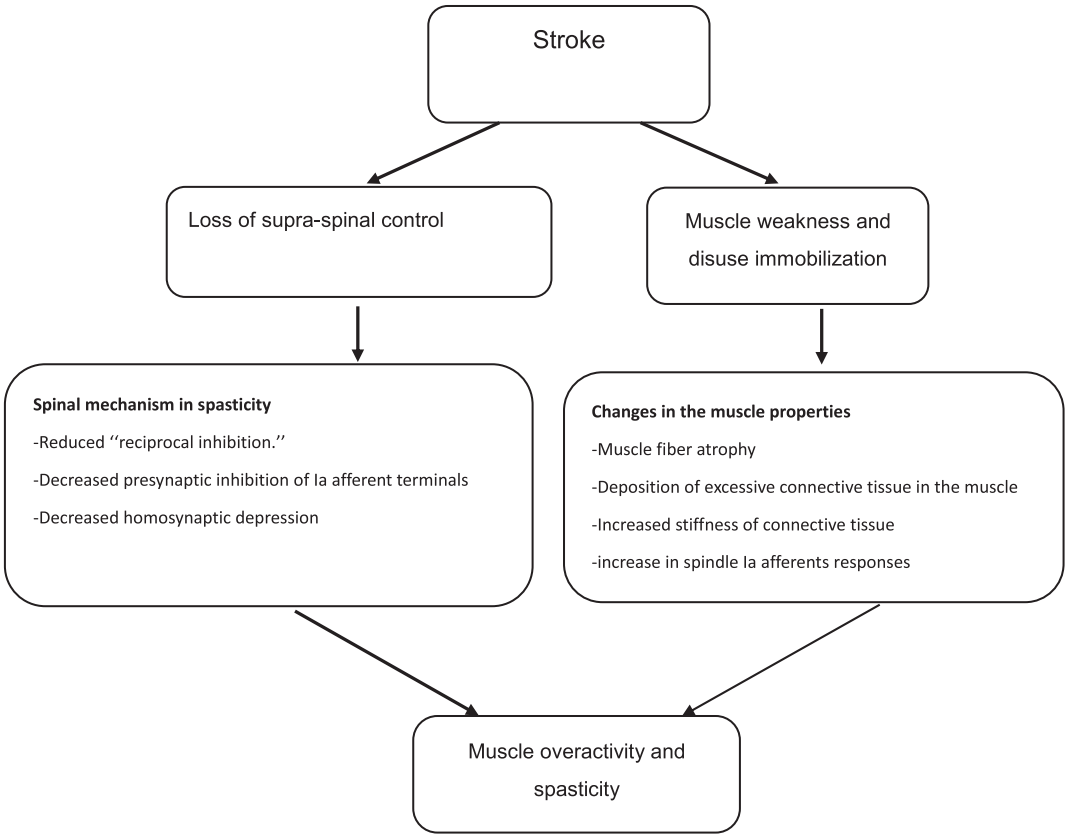

Fig. 1. Potentia mechanisms involved in spastic movement disorder.

patients become more aware of their reactions to such triggers, they can help the healthcare professional with the ongoing management of their spasticity.[30]

Stretching of the involved muscle is the commonly used physical modality for the management of spasticity. Prolonged and regular stretching can reduce sarcomere shortening, and help increase or preserve the length of the muscles and other musculoskeletal structures.[31] Fitting of splints/braces, and occasionally, serial casting, is performed to achieve a goal similar to that of stretching, and to improve performance in functional tasks (e.g., ankle foot orthosis to correct foot drop due to plantarflexor spasticity).[32]

Neuromuscular electrical stimulation, when applied to an agonist muscle, was shown to decrease spasticity in the antagonist muscle, although the effect was short-lived. These effects can be explained by the inhibition of interneurons, which can also reduce nociceptive inputs according to the gate control theory. Several systematic reviews have concluded that spasticity reduction and improvement in the range of movement is observed in stroke survivors with the applications of neuromuscular electrical stimulation, combined with other interventions.[33] Other methods, such as extracorporeal shock wave therapy, transcranial and spinal cord magnetic stimulation and electro-acupuncture, used in combination with conventional routine care, have also shown positive effects in spasticity management.[34–38]

Surgical treatment of spasticity is mainly used for severe cases, or for the after-effects induced by spasticity that lead to functional impairments. Muscle-tendon lengthening can decrease spasticity by altering the tension-to-length relationship of the contracting muscle. Techniques for destroying nerves, such as neurectomy, rhizotomy, and myelotomy, can also be used to control spasticity, but these are typically reserved for the most recalcitrant cases.[39]

7. Pharmacological treatment

Pharmacological treatment can affect the central nervous system or peripheral muscles to reduce spasticity, and can be administered by oral or injectable forms. The dosage and form of pharmacological treatment depend on the patients' disabling symptoms and tolerability of adverse effects, and usually starts with the least invasive form, following a stepladder paradigm (Table 1).

8. Oral forms

Baclofen is the most common oral treatment against spasticity. Baclofen is an analog of gamma-aminobutyric acid (GABA), and can cross the blood-brain barrier at the spinal cord level, and binds to $GABA_B$ receptors, reducing the release of excitatory neurotransmitters and substance P. Some studies have found that baclofen improves clonus, frequency of flexor spasm, and range of joint movement, resulting in improved function. The adverse effects of Baclofen include sedation, general fatigue, and hepatotoxicity, so regular monitoring of liver function is recommended for patients with long-term usage. Abrupt disruption of baclofen usage may cause withdrawal symptoms, including rebound spasticity, seizures, hallucination, rhabdomyolysis, and even multisystem organ failure, and these symptoms can be avoided by tapering off the usage gradually.[40]

Tizanidine is an alpha 2-adrenergic agonist which activates presynaptic motor neurons and reduces muscle tone. Common adverse effects of this agent include sedation, dizziness, hypotension, nausea, and dry mouth. Some studies have suggested that tizanidine has analgesic properties, in addition to its antispasticity

Table 1
Mechanism of action and side-effects of pharmacological treatment of spasticity.

Drug	administration	Mechanism	Common side effects
Baclofen	oral	GABA analog binds to $GABA_B$ receptor and inhibits muscle stretch reflex	Sedation, dizziness, weakness, fatigue, hepatotoxicity, psychosis
Tizanidine	oral	Centrally acting alpha-2 noradrenergic agonist; inhibit release of excitatory neurotransmitters in the supra-spinal level	Sedation, dizziness, mild hypotension, hepatotoxicity, dry mouth
Benzodiazapines	oral	Increase the affinity of GABA for $GABA_A$ receptor leading to inhibition and reduction of synaptic reflexes	Sedation, weakness, hypotension, adverse GI effect;
Dantrolene	oral	Interferes with release of calcium from sarcoplasmic reticulum in muscles	Hepatotoxicity, muscle weakness
Gabapentin	oral	GABA agonist	Fainting, somnolence, nystagmus, ataxia, sedation.
Phenol/alcohol	injectable	Chemical denervation of the muscles	Dysesthesias, damage of the sensory nerves and pain;
Botulinum toxin	injectable	Inhibit acetylcholine release at neuromuscular junction	Local pain, fever, rarely swallowing problems; antibody formation

effects.[41] Tizanidine is a short-acting muscle relaxant, so there are fewer issues related to muscle weakness; however, frequent dosing is required to maintain spasticity control.

Benzodiazapines, such as diazepam and clonazepam, can bind in the brainstem and at the spinal cord level, and enhance the affinity of GABA for the $GABA_A$ receptor complex. This results in an increase in the presynaptic inhibition, and subsequent reduction of monosynaptic and polysynaptic reflexes.[42] The adverse effects of benzodiazapines include sedation, weakness, hypotension, and adverse gastrointestinal effects. However, these drugs also produce tolerance and dependence, limiting their long-term usage. In addition, a study has shown possible detrimental effects of benzodiazapines on post-stroke motor function; therefore, it is not currently recommended for spasticity management in stoke patients.

Dantrolene sodium acts on peripheral skeletal muscles rather than nerves. The drug reduces muscle contraction by affecting the release of calcium from the sarcoplasmic reticulum of the skeletal muscles.[43] Caution should be exercised during the use of this drug since there have been reports of associated liver failure. As dantrolene does not selectively target specific muscles, it may lead to the adverse effect of general muscle weakness. In some rare cases, it has been reported to be fatal in high doses, and is, therefore, not considered a first-line drug.

Gabapentin, a GABAergic drug modulating intracellular calcium channels, was introduced as an anti-epilepsy drug. Some studies have shown that the use of gabapentin alone, compared to a placebo, demonstrated a reduction in the spasticity.[44] The adverse effects include somnolence, tremor, and nystagmus. Gabapentin is not a first-line treatment for spasticity, and is rarely used for monotherapy.

9. Neurolysis

Phenol and alcohol can reduce spasticity by chemical neurolysis. A 3–5% concentration of phenol can cause axonal degeneration and motor fiber demyelination, and 35–50% alcohol can cause small fiber demyelination.[45] Possible adverse effects include pain and swelling at the site of injection. In a very small number of patients, dysesthesias may occur if injections are administered near sensory-rich nerve branches.[46]

Botulinum toxin type A acts on the neuromuscular junctions, inhibiting the exocytosis of acetylcholine from presynaptic nerve terminals.[47] Compared to phenol and alcohol, intramuscular botulinum toxin type A injection inhibits selective muscle contraction without undesired general weakness and sedation, and the effect of botulinum toxin type A is reversible, lasting for 3–4 months.[48] Several reviews have concluded that botulinum toxin type A injection is safe and effective in reducing post-stroke spasticity.[49] The adverse effects of botulinum toxin type A are local pain, fever, and rarely, transient urinary incontinence or dysphagia, due to dissemination to other body parts. Injection of botulinum toxin type A is the recommended first-line treatment for regional spasticity affecting the upper limb in patients with stroke.[50] This might induce muscle weakness, and is associated with high cost and invasiveness. Additionally, the formation of neutralizing antibodies might attenuate the treatment effect.[51]

10. Conclusions

A significant proportion of stroke survivors present with spasticity. Post-stroke spasticity might have an impact on comfort, posture, ease of care, and function, and may increase the risk of comorbid complications, such as contractures and skin ulcers. By understanding the pathophysiology and clinical manifestation of spasticity, physicians can select the most effective and appropriate approach for its management. There are several approaches to control spasticity, including non-pharmacological and pharmacological treatments, and are usually combined in clinical practice. The goal of spasticity management is to avoid complications, and to increase functional abilities and improve the quality of life. Also, further research on the prevention of post-stroke spasticity is necessary to improve stroke survivors function and quality of life.

Conflict of interest

None.

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