Artículo de revisión

Espasticidad, nuevos conceptos fisiológicos y patofisiológicos aplicados a la clínica

Spasticity, novel physiologic and pathophysiological concepts applied to clinic

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Resumen

La espasticidad muscular es un signo descrito desde hace siglos. Sin embargo, esta revisión pretende analizar el significado y clarificar la visión de lo que hace que se asiente en la práctica clínica, para diferenciar entre un paciente con espasticidad de quien no la presenta. La espasticidad es una manifestación clínica que se produce secundariamente a una afectación motora del sistema nervioso, a cualquier nivel. Se define como un aumento del reflejo de estiramiento muscular el cual depende del movimiento muscular para su manifestación. Existen diversos mecanismos patogénicos implicados en este trastorno, incluyendo una mayor excitación neuronal y una disminución de las inhibiciones neuronales, que traen como consecuencia, hiperreflexia e hipertonía. La espasticidad muscular es el resultado del efecto de los diferentes eventos que ocurren en el sistema nervioso central, como traumatismos, enfermedades desmielinizantes, tumores, isquemia, radiación etc. El daño principal se produce en el tracto piramidal, siendo poco claro el papel de otras vías.

Palabras clave: médula espinal, nervous system, tronco cerebral, hipertonía muscular, espasticidad muscular

Abstract

Muscle spasticity is one of the signs described since centuries ago. Nevertheless, this review pretends to analyze the meaning and clarify the vision of what does it stand for in clinical practice, to differentiate between one patient with spasticity from one that does not. Spasticity is a secondary symptom to a motor insult of the central nervous system, in the spine, or in the pyramidal system in the encephalon. It is defined as an augmentation of myotatic reflex or muscular stretch reflex that depends of the muscular movement for its manifestation. Pathogenic mechanisms involved in this disorder include an increased neuronal excitation (due to glutamate and aspartate excess) and a decreased neuronal inhibition (due to shortage of gamma-amino butyric acid) that bring as consequence, hyperreflexia and/or hypertonic muscular reflex. Spasticity is the result of the effect of different events including trauma, demyelinating diseases, tumors, stroke, radiation, etc. Main damage is caused to the pyramidal tract, but is not clear the role of others anatomical pathways.

Keywords: spinal cord, nervous system, brainstem, muscle hypertonia, muscle spasticity

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Introduction

Spasticity is a well known sign describe since the nineteenth century and it is not only the resistance to initial passive movement, as it is wrongly known. This review aims to clarify the gaps on the topic. To understand spasticity, is imperative to recognize the anatomy, physiology and pathophysiology of the central nervous system and the skeletal muscle, the correlations between them and their damage, learning the impact on the clinical aspects. It is important to emphasize that spasticity is the main sign of clinic feature in many diseases affecting the central nervous system, primarily the pyramidal pathway. The result of this injury is hypertony and hyperreflexia with an inability for suitable mobilization of the extremities that can be very disabling, making crucial in its study and understanding to obtain additional diagnostic and therapeutic measures, always with the objective of improving patient's quality of life.

Anatomy

The pyramidal tract gets its name due to the formation of the pyramids on the ventral portion of the medulla oblongata in the brainstem, consisting of the anterior corticospinal, lateral corticospinal and corticonuclear or geniculate tracts, which together are often called upper motor neuron. It is formed approximately by one million fibers, mostly fine myelinic fibers, that has the highest conduction speed in the human body (120 m/sec), and a very small percentage of amyelinic fibers (Kim & Pope, 2005). Fifty to seventy-five percent of the fibers of the pyramidal tract originate in the ascending frontal gyrus of the primary motor and premotor cortex, anterior to the central sulcus, and the rest come from posterior areas in the parietal lobe, the primary sensitive area. The axons of the corticospinal tract get together, forming the *corona radiata*, and descending through the posterior limb of the internal capsule into the middle two-thirds of the cerebral peduncles of the midbrain. In this descent, the fibers remain somatotopically organized but their position is shifted: in the *corona radiata*, the fibers from the face become located anteriorly, with the arm in the middle and the leg remains posteriorly with respect to the anterior horn of the lateral ventricle; the *corona radiata* and the posterior limb of the internal capsule are essential locations because they are correlated to reduced motor outcome (Kim & Pope, 2005; Marx, Klannetti, Thoemke & 2005; Jang, 2009). This orientation persists in the posterior limb of the internal capsule. In the cerebral peduncle, the fibers representing the face become most medial, whereas those of the legs become most lateral. The corticospinal fibers become less recognizable as a tract as they course through the ventral portion of the pons. They form bundles interspersed with a variety of other descending and crossing white matter tracts. The somatotopic arm/leg distribution is abruptly broken down, but there remains a somatotopical order for fibers controlling proximal versus distal muscle groups. The corticospinal fibers controlling proximal muscles is located in the dorsal basis points meanwhile the fibers controlling distal muscles get more ventral. (Marx, Klannetti & Thoemke, 2005) When the fibers enters into the medulla, they create a very discrete, easily recognize bundle on the ventral aspect of the medulla known as the *pyramids*. Because it is such an easily recognizable bundle of nerve fibers, the corticospinal tract is often referred as the *pyramidal tract*, although the pyramids also con-

tain fibers other than those in the corticospinal system. The corticospinal tract is the most important motor pathway in the human brain (Jang, 2011).

About 80% of the fibers have a contralateral course, crossing over at the pyramids, forming the *lateral corticospinal tract*, which is responsible for the distal musculature of the extremities. The rest of the fibers continue as the *direct* or *anterior corticospinal tract* that runs through the anterior funiculus of the spinal cord in its medial region, responsible for the axial musculature. They both finish at cervical and thoracic level of the spinal cord with predominance of the lateral corticospinal tract on the slides IV-VIII of Rexed (Cuadrado, Navalón, Palomar & Linares, 2001). Actions of corticospinal neurons are much more potent on contralateral than on ipsilateral limb motoneurons, showing the predominant crossed projections of these neurons (Stecina & Janokowska, 2007; Phillips & Porter, 1997). For many years, little information had been known about uncrossed pyramidal tract. Nonetheless, these fibers have been shown to terminate in the intermediate zone and the ventral horn (Lacroix, Havton, McKay, Yang, Brant & Roberts, 2004) within spinal cord regions, where several populations of premotor interneurons are located and therefore these cells might be activated by ipsilaterally descending pyramidal tract neurons (Stecina, Janokowska, Cabaj, Petterson, Bannatyne & Maxwell, 2008) (see Figure 1).

Besides the pyramidal tract anatomy, it is important to know the neurotransmitters involved in this system, as an impaired neurochemistry may lead to functional disorders at any level. Histochemical techniques have been used since the 40's to 60's to identify the substances involved in the transmission of the neuronal signals (Stone, 1973) in the pyramidal tract and it has been proved that it is not cholinergic nor aminergic (dopaminergic or noradrenergic) substances (Koelle, 1954; Carlsson, Falck & Hillarp, 1962) but glutamate (Stone, 1973), be the neurotransmitter present in the cerebral cortex in larger concentrations than in any other areas of the central nervous system (Berl & Waelsch, 1958). This is important in spasticity, as there is an imbalance between excitatory and inhibitory neurotransmitters as described in the Pathophysiology section. To protect the fidelity of descending commands during centrally initiated movement, afferent input to the spinal cord can be suppressed by presynaptic control of transmitter release during movement. This mechanism may allow the nervous system to gate peripheral reflexive input to motoneurons (Jackson, Baker & Fetz, 2006; Hultborn, Meunier, Pierrot-Deseilligny & Shinodo, 1987).

The pyramidal pathway is responsible of the voluntary movements of the body both the gross, performed by the proximal muscles of the limbs, and the fine movement made by the distal musculature. However, besides the stimulus from corticospinal neurons, nuclei located at the brainstem (such as the rubro-spinal, reticulo-spinal and vestibulo-spinal) also discharge during movement, (e.g. walking), as the destruction of these neurons may affect movement precision (Armstrong & Drew, 1984). At the same time, the pyramidal tract has a sensory and vegetative control in the body. The injury at any level of the track can be caused by various pathologies (see Table 1), many of which may manifest with spasticity. (Bradley, 2004)

Figure 1. A: Origin and course of the pyramidal tract in the precentral gyrus and other areas of the cerebral cortex. It is shown its course through the telencephalon. In the internal capsule, fibers with destination at the cervical region are rear the arm's and lower limb's fibers. This order changes in the brain stem and spinal cord. B: Origin, course and ending of the rubrospinal and reticulospinal tracts.

Figure 2. Schematization of the monosynaptic rotulian reflex, prototype of the muscular stretch reflex. An applied stimulus travels through the afferent sensory nerve type Ia, originated in the muscle spindle, and enters the dorsal horn of the spinal cord. It contacts the interneurons and makes synapse with the efferent neurons of the ventral horn. These ones innervate the muscle, whose response is the immediate extension. At the same time, neurons that ascend in the spinal cord, make synapse in the thalamus to deliver information to the cortex and finally make the stimulus conscious.

Spasticity

It was defined by Lance in 1980 as: "A motor disorder characterized by a velocity-dependent increase in muscle stretch reflex, also called miotatic reflex, with exaggerated movements in the tendons, which is associated with hypertonia and hyperreflexia, due to the neuronal hyperexcitability as one of the signs of upper motor neuron syndrome" (Lance, 1980).

Spasticity is part of a spectrum of voluntary motor activity, broadly characterized as spastic hypertonia (Meythaler, 2001). It can include hyperactive multipoint reflexes (spasms), and in some cases could be accompanied by dystonia, that means simultaneous contraction of agonist and antagonist muscles without continued hypertonia, or abnormal posturing (Hornby, Kahn, Wu & Schmit, 2006). Indeed, is frequently to confused spasticity and dystonia in patients with cerebral palsy that settled both signs.

Physiology

Miotatic or muscle stretching reflex. Anatomic and physiological units called spindles compose muscles. By exciting the muscle spindles and increasing the length of the muscle fibers, large fibers surrounding the spindle contract by reflex. Anatomically, a type Ia sensory fiber that comes from the spindle, enters the dorsal horn of the spinal cord and makes direct synapse with neurons of the ventral horn, which innervate the muscle fibers that originated the initial stimulus. Under normal conditions, the miotatic reflex has a low activity, which is triggered by slight excitability of motor neurons, whose threshold is low and trigger an afferent discharge that produces a presynaptic inhibition by means of Ib fibers (Lance, 1980; Nielsen, Petersen, Crone & Sinkjaer, 2005) (see Figure 2).

In voluntary contraction, all of this increases with the difference that the inhibitions produced by Ia and Ib fibers decrease. Miotatic reflex activity is high. In contrast, in spasticity, the presynaptic inhibition of Ia and Ib is reduced, and miotatic reflex activity is increased during voluntary contraction (Katz & Rymer, 1989).

Hypertonia

Muscle tone is the resistance to stretching of the muscle, thus its increase is called hypertonia. Sometimes it is defined spastic muscle as one with high resistance to stretching due to hyperactivity of stretch reflexes. Thus, the muscle tone is the sustained muscle contraction that even at rest is present with a small fiber recruitment, which means that the person is in a basal state of contraction, the normal tone (Katz & Rymer, 1989; Gregson, Leathley, Moore, Smith, Sharma & Watkins, 2000). When there is a disease of the lower motor neuron, the tone is decreased, flaccid or depressed, and it is hypotonic. In contrast, upper motor neuron with spasticity presented a mild to severe increase, which may be expressed as "hardness" of the muscle that increased dramatically when the velocity of the movement is higher, recruiting more muscle fibers. Clinically, this part of the sign is presented in practically all the cases (Burke, 1988; Gordon, Keller, Stahinko, Hoon & Bastian, 2006).

Table 1. Summary of the most frequent causes of the pyramidal tract injury: congenital, acquired and genetic.

Congenital	Acquired	Genetic
Cerebral palsy children	Cranioencephalic trauma, hemorrhage (blood pressure, brain aneurysm, atherosclerosis, arteriosclerosis), transient cerebral ischemia, hemisphere lesions by radiation therapy, embolization, thrombosis, vasculitis, multiple sclerosis, brain abscesses, tumors, granulomas, meningoencephalitis.	Progressive supranuclear palsy, family spastic paraplegia.

Table 2. Characteristic of positive and negative signs of upper motor neuron affection.

Positive signs	Negative Signs
Spasticity	Decreased strenght
Hiperreflexia	Decreased motor control
Primitive reflexes	
Babinski +	Decreased cordination
Clonus	
Sincinesias	

Hyperreflexia

Hyperreflexia is defined as the increase or exaltation of reflexes. In the nervous system, reflexes are transmitted via signals through action potentials, which are changes in membrane potential at very high speeds that are spread across the membrane of the nerve fiber. These begin with an abrupt change of the resting potential from negative to positive to reach the "threshold" to achieve stimulation and start driving of a nerve signal. In spasticity, physical exploration shows patients with reflexes augmentation of the involved limb, inclusive an extreme exaltation could be traduced how clonus. Not always the spastic patient showed hyperreflexia, it presence affirmed the diagnosis, but the absence is not excluded it.

Upper motor neuron syndrome

Upper motor neuron syndrome can be described as an injury that occurs in the upper levels of the central nervous system, either motor cortex or brainstem, but inclusive spinal cord tracts. Following brain or spinal cord injury, a prominent feature of the upper motor neuron syndrome generates spasticity (Sheean, 2002). The clinical syndrome resulting from an upper motor neuron lesion depends more upon its location and extent, and the time since it occurred, than on the pathology of the lesion (Sheean, 2002). The results define what is known as positive signs and negative signs of the pyramidal syndrome (see Table 2). Positive signs are in excess during sleep and negative ones decreased during it.

Table 3. *Most used clinical scales to measure spasticity.*

Asworth Scale
0 Normal Tone
1 With slight increase of tone (catches and releases)
2 Marked increase in tone and hyperreflexia in the part that move with more ease
3 Increase in muscle tone with difficulty in passive movements
4 Hypertonic degrees than in flexion and extension
Bohannon Scale (modified ashworth)
0 Normal tone
1 With slight increase of tone. Minimum detention mobilization, with resistance at the end of the arc
1 + With slight increase of tone. Minimum detention mobilizing resistance in less than half of the arc
2 With moderated increase of tone
3 With severe increase of tone
4 With hypertonia at maximum degree
Tardieu Scale
0 No Hypertonia
1 Hypertonia with opposition to movement
2 Hypertonia with cogwheel sign
3 Hypertonia with exhaustible clonus
4 Hypertonia with inexhaustible clonus

Spasticity and rigidity

Anatomically, the difference lies in alterations in the basal ganglia which is typical of rigidity, but the spasticity is classically described as pyramidal tract injury, including other structures as reticular and parapyramidal areas.

Spasticity is characterized by muscle spasms, mostly in the distal and proximal portions of limbs, with preference of arms, hands, fingers and knees. Clinically there is hypertonia, increased flexor tone that is resistant to extension at the start of the movement and gives up at the end (which causes the phenomenon known as razorblade hypertonia); hyperreflexia, clonus, jerks or myoclonia (Tarsy & Simon, 2006; Taricco, Pagliacci, Telaro & Adone, 2006), a positive Babinski sign, sleep disorders; cutaneous abdominal and cremasterian reflexes are absent on the side of the injury, neuronal hyperexcitability, and sudden changes in posture. Also occurred weakness and motor uncontrolled. In addition, spasms may produce pain crises (Filipetti, Decq, Fontaine, Feve, Pirotte & Barbedette, 1998; Priebe, Sherwood, Thornby, Khars & Makowski, 1996). Table 3 defines the damaging effects of spasticity classified according to the International Classification of Functioning (ICF).

In contrast, rigidity is defined as an increase in muscle resistance to passive movement. It is presented throughout the whole's movement duration to what is known as "plastic hypertonia". It shows the "cogwheel" phenomenon. Unlike spasticity, rigidity is observed in both flexor and extensor muscles. It is produced by supra-segmental activation of spinal reflex mechanisms, increasing the discharge of alpha motor neurons, due to a pallidal activation and altered dopaminergic activity. In both cases, there is an increase in muscle tone that gives it the clinical "hardness" and sometimes, as in cases of infantile paralysis, can coexist and is difficult to distinct one from another (Lang & Lozano, 1998; Nussbaum & Ellis, 2003).

Pathophysiology

After neurological injury, it has been demonstrated there are changes in passive muscle stiffness (Brown, 1994). The origin of the pathology and primary mechanisms of stretch reflex hyperexcitability is primarily neural. Two of these mechanisms are: 1)

Alterations in motoneuronal excitability (Dietz & Sinkkjaer, 2007), and 2) Augmented synaptic inputs with muscle stretch (Dietz, Quintern & Berger, 1981). However there are also intrinsic changes in the passive mechanical properties of muscle after spasticity, as well as changes within the extracellular matrix that contribute to the overall changes in the tissue, such as a decreased passive tension in fiber bundles. This supports the theory that, although spasticity is multifactorial and neural in origin, significant structural alterations in muscle also occur at long time (Iles & Roberts, 1986).

It has been shown in animal models that direct injury of the corticospinal tract does not lead to spasticity, but a flaccid paralysis accompanied by hypotonia, in which exist pathological reflexes, but no spasms or hyperreflexia, and it is not until a period of 6 weeks later when spasticity presents. For this reason, the transition from a flaccid to spastic hemiplegia is a matter of controversy, and thus, the injury of the pyramidal pathway is not entirely clear in relation to the presence of spasticity, so it is thought that damage to para-pyramidal pathways may be a possible cause of this disorder. It is certain that injury will always be limited to the central nervous system: motor cortex, internal capsule, brainstem or spinal cord (Lieber, Runesson, Eliarsson & Friden, 2003; Lieber, Steinman, Barash & Chambers, 2004). Nowadays, importance has been given to other nerve tracts that form the internal capsule as part of this disorder's etiology. Reticulospinal bundle runs along the corticospinal tract in the internal capsule. Among its functions, medial fibers inhibited muscle reflexes and tone, and lateral fibers, on the contrary, facilitate extensor tone.

That is why there is doubt about the accuracy of the pyramidal pathway as the exclusive responsible of the spastic abnormality (Conway, Hultborn, Kiehn & Mintz, 1988; Kiehn & Eken, 1998). Furthermore, in animal models it has been demonstrated that an injury of the reticulospinal bundle may be the main cause of the spasms due to a loss of inhibition of muscle stretch reflexes, which cause their increase. Moreover, it is believed that other pathways, such as the lateral vestibulospinal tract have to do with spasticity, so has been used the section on surgical methods to reduce the intensity of this condition, but whose function is not entirely clear at present (Tarsy & Simon, 2006).

Additionally, studies in spastic mice demonstrate a motor phenotype, caused by a naturally occurring mutation in the glycine receptor (GlyR) (Graham, Brichta, Schofield & Callister, 2000). The spastic phenotype is also associated with alterations in the binding sites for the inhibitory amino acid GABA and the modulatory site for the benzodiazepines (Biscoe & Duchen, 1986). This mutation causes decreased transcriptional efficiency of the GlyR β subunit (Kingsmore, Giros, Suh, Bienarz, Caron & Seldin, 1994), and thus a reduced expression of the adult form of the GlyR throughout the nervous system (White & Heller, 1982), specifically in the ventral horn of the spinal cord. In mammalian spinal motoneurons with spasticity, it has been observed changes in their intrinsic properties. One of them is the presence of persistent inward (Ca²⁺ and Na⁺) currents, which may be partly responsible for the spastic behaviors (Verrotti, Greco, Spalice, Chiarelli & Iannetti, 2006). These currents are facilitated by serotonergic and noradrenergic influx from brainstem pathways (Goldstein, 2001; Graham, Schoefield, Sah & Callister, 2003). These findings suggest that mutations may be the cause of spasticity in sensory regions responsible for

nociceptive transmission. As a consequence of these mutations, there is an increase of GABAergic transmissions in the spinal cord, which inhibits neuronal plasticity in the mouse (Graham, Schoefield, Sah & Callister, 2003). The stimulus results in a reduced need for continuous synaptic afference during sustained voluntary contractions (Li & Bennett, 2003). Evidence suggests an increase of excitatory neurotransmitters such as glutamate and aspartate, as well as the decrease in inhibitory ones such as GABA, glycine and taurine in the spinal cord spasticity mechanism. There is also an alteration in alpha motor neuron with apparent decline in the dendritic buttons of these neurons and in branching of others, which only shows in a group of muscle fibers (Bhakta, 2002; Rodríguez-Mutuberría, Serra-Valdés, Pérez Parra & Palmero-Camejo, 2004). Therefore, spasticity may be the result of an imbalance between excitatory and inhibitory actions of spinal motor neurons (Decq, 2003; Sherwood, Graves & Priebe, 2000; Tardieu, 1980).

Actually, it is known that in an injury that affects the pyramidal pathway, discharges of the neuromuscular spindle to its muscle decrease, even though spasticity appears on the following weeks. However, there is the hypothesis of an hyperexcitation of the alpha motor neurons due to a decreased function of the para-pyramidal tracts affected by the injury, that run along the spinal cord and end in axon-axon synapses, therefore reducing the amount of inhibitory neurotransmitter (mainly GABA) released by the neurons, thereby inhibiting their excitatory reflex. This leads to an increase in retrograde conduction of the neuron to the muscle, therefore increasing tendon reflexes. It is believed that there is a *decrease in the germination* of synaptic buttons that lead to spasticity; this theory is known as the unbalance theory. In the same way, it is proved that the inhibitory action of Golgi tendon organs is decreased in patients with spasticity (Barboi & Barkhaus, 2004). When spasticity produces clinical incapacity by delaying with posture, motor capability or daily living activities, medical management is recommended. A pharmacological method relies on the use of medications which regulate neurotransmitters performing at the cortico-spinal level (GABA, glycine, glutamate, noradrenaline, serotonin). The purpose of this treatment is to reduce spinal reflex excitability by decreasing the deliverance of excitatory neurotransmitters, or by potentiating the activity of inhibitory inputs. Evaluation of the efficiency of these medicines is determined by the curative objectives.

Clinimetric

There are several ways to assess spasticity, not only in terms of neurophysiology, but also clinically. The first one to measure hypertonia was Tardieu, with a proffer based on the physiological activity of muscle and reflexes, which refers to the speed it is measured with. Subsequently, Ashworth suggested a more static hypertonia scale in an attempt to measure changes in spasticity. Originally, was probed after the use of carisoprodol in patients with multiple sclerosis, but now is wide spread for other causes of spasticity. Nowadays, studies have demonstrated that the Modified Ashworth Scale produces reliable measurements in the assessment of different muscle groups with spasticity (Lin, Chan, Pierrot-Deseilligny & Burke, 2002; Skold, Harms-Ringdhal, Hultling, Levi & Seiger, 1998; Haas & Crow, 1995; Lima, Pupio, Lima, De Freitas, Regina-Ribeiro, Tortoza & Gomes-Lucareli). However, studies and reviews suggest

the Tardieu Scale to be a more properly clinical measure of spasticity than the Ashworth or modified Ashworth Scales, as it appears to adhere more closely to Lance's definition of spasticity since it involves assessment of resistance to passive movement at both slow and fast speeds (Schule, Holland, Klimpe, Kassubek, Klopstock & Mall, 2006). Whatever the best spasticity assessment scale, they can be used alone or in combination. (Table 4)

Conclusions

Spasticity is the result of a neurological injury in the pyramidal and parapyramidal systems that extend from the brain to the spinal cord. There is an increase in muscle tone and/or muscle stretch reflex, resulting in compensation for caused damage. This is what makes spasticity different from other signs such as rigidity. There are multiple mechanisms involved in the understanding of spasticity, such as a lack of inhibition and over-excitation. The main problem presents when this physiological spasticity becomes pathological (inauspicious) and over time disastrous, which ends with deformity of the limbs and therefore alterations in personal hygiene, welfare of position and walking, and even people's quality of life.

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