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The pathophysiology of spasticity

G. Sheean

Department of Neurosciences, Medical School, University of California – San Diego, CA, USA

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Spasticity is only one of several components of the upper motor neurone (UMN) syndrome, known collectively as the 'positive' phenomena, that are characterized by muscle overactivity. Other components include tendon hyper-reflexia, clonus, the clasp-knife phenomenon, flexor and extensor spasms, a Babinski sign, and spastic dystonia. Spasticity is a form of hypertonia due to hyperexcitable tonic stretch reflexes. It is distinguished from rigidity by its dependence upon the speed of the muscle stretch and by the presence of other positive UMN signs. Hyperactive spinal reflexes mediate most of these positive phenomena, while others are due to disordered control of voluntary movement or abnormal efferent drive. An UMN lesion disturbs the balance of supraspinal inhibitory and excitatory inputs, producing a state of net disinhibition of the spinal reflexes. These include proprioceptive (stretch) and nociceptive (flexor withdrawal and extensor) reflexes. The clinical syndrome resulting from an UMN lesion depends more upon its location and extent, and the time since it occurred, than on the pathology of the lesion. However, the change in spinal reflex excitability cannot simply be due to an imbalance in supraspinal control. The delayed onset after the lesion and the frequent reduction in reflex excitability over time, suggests plasticity in the central nervous system. Knowledge of the electrophysiology and neurochemistry of spinal reflexes, together with the action of antispasticity drugs, helps us to understand the pathophysiology of spasticity.

With any discussion on spasticity, it is helpful to begin with the pathophysiological basis of this condition. Understanding the mechanisms of the patient's clinical symptoms is a great help in their management. It can assist in determining the sort of therapy that they should be given. Although it is a complex subject, having a good grasp of the scientific basis of spasticity, is very rewarding.

Upper motor neurone syndrome

Upper motor neurone (UMN) syndrome is familiar to most people working in this field; it has two classical distinctions in terms of its signs or symptoms. The negative signs, are weakness and loss of dexterity, for example after a stroke. The positive features are characterized by muscle overactivity, either excessive muscle contraction or some sort of inappropriate muscle activity. Spasticity is only one of those positive features; others are hyperactive tendon reflexes, clonus and flexor spasms. All of these characteristics are frequently and unfortunately referred to as 'spasticity', which has become something of a generic term for any or all of these positive features.

How do these positive symptoms come about? They can be divided into three main areas. Firstly, spinal reflexes: abnormal processing of spinal reflexes contributes to most of the positive features of the UMN syndrome. They are all afferent-dependent, relying upon some sort of sensory feedback from the periphery, like muscle stretch, pain or cutaneous stimulation. Secondly, there are efferent drives that do not depend entirely upon peripheral afferent feedback, although they may be driven by reflex activity higher in the central nervous system. The third group of the positive UMN signs are the various disorders of voluntary muscle movement. There is much overlap with the negative features, but this paper will focus more on the positive side, that is, features characterized by muscle overactivity.

Table 1 illustrates one approach to classifying the forms of muscle overactivity in the UMN syndrome. These categories separate the clinical features of the UMN syndrome into neat pathophysiological groups, in a way that could help to determine therapy. Stretch reflexes are proprioceptive reflexes, and are either tonic (from a sustained stretch, as in resting muscle tone), or phasic (from a short stretch, as in deep tendon reflexes). Other related features in this category are clonus and

Correspondence: Dr G. Sheean, Department of Neurosciences, Medical School, University of California – San Diego, San Diego, CA, USA (tel.: +1 619 543 6291; e-mail: gsheean@ucsd.edu).

Table 1 Classification of the forms of muscle overactivity in the UMN syndrome

Spinal reflexes	Efferent drive	Disordered control of movement
Stretch Nociceptive Cutaneous	Spastic dystonia? Associated reactions?	Co-contraction

irradiation of reflexes. Flexor and extensor spasms are nociceptive reflexes. The most familiar of the cutaneous reflexes is the Babinski sign.

As the name implies, the clinical components of the UMN syndrome are due to a lesion of the upper motor neurones. Upper motor neurones include supraspinal inhibitory and excitatory fibres, which descend to the spinal cord, exerting a balanced control on spinal reflex activity. Included are the pyramidal fibres, but studies in animals have shown that a pure pyramidal lesion causes only minimal neurological deficits, the so-called pyramidal syndrome. There is some clumsiness, particularly in distal hand muscles, a small amount of weakness, initial depression of deep tendon reflexes, followed by some exaggeration of deep tendon reflexes and a Babinski sign. Spasticity and other forms of muscle overactivity do not occur. Similarly, most of the weakness that occurs in say, a stroke, is not due to a lesion of the pyramidal fibres, but of other UMN fibres which travel very closely with them. I call these upper motor neurones 'parapyramidal', rather than 'extrapyramidal', which has basal ganglia connotations.

The UMN syndrome, both positive and negative features, is largely due to parapyramidal fibre dysfunction, with some contribution from the pyramidal fibres. Isolated lesions of the pyramidal tract do not cause spasticity. A recent paper (Sharman *et al*., 2000) described a man who had a lacunar stroke, apparently caus-ing a lesion of the pyramidal fibres alone. It caused no spasticity, but there was some slight tendon hyperreflexia and a Babinski sign. This observation validated those experimental lesions performed in cats and in humans, where no spasticity was seen. So, pyramidal fibres play a small role in the UMN syndrome. The excitability of spinal reflexes is under supraspinal control, both inhibitory and excitatory, partly by these upper motor neurones.

The main tract that inhibits spinal reflex activity is the dorsal reticulospinal tract, which arises in the ventromedial reticular formation (Figure 1). It runs very close to the lateral corticospinal tract, the so-called pyramidal tract. Thus a single lesion frequently affects both tracts and produces a clinical picture reflecting the combined lesion. The pyramidal tract lesion makes a small

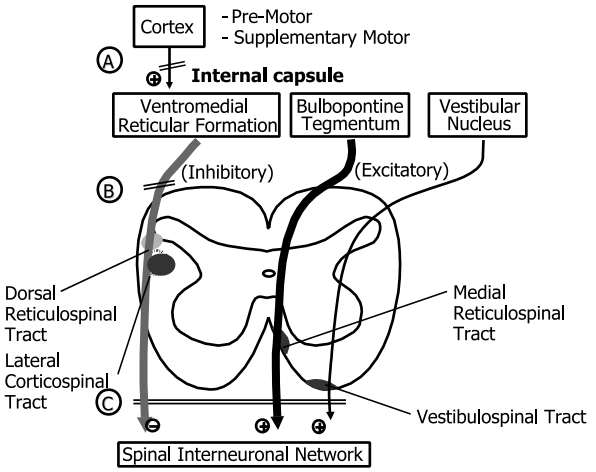

Figure 1 The major descending pathways controlling spinal reflex excitability. The inhibitory fibres are shown in grey.

contribution, but the parapyramidal dorsal reticulospinal tract produces most of the symptoms and signs.

The excitatory pathways also arise in the brain stem; the most important are those arising in the bulbopontine tegmentum. These neurones descend in the medial reticulospinal tract. The vestibulospinal fibres also have an excitatory effect upon spinal reflexes, but tend to be somewhat separate from the other excitatory pathways and do not seem to be as important in the production of spasticity.

The fact that there is a balanced system of inhibition and excitation, and that the fibres run in different areas of the spinal cord, presents opportunities for lesions to affect one fibre tract and not another. It is the mixing and matching of lesions that leads to a variety of clinical syndromes. Furthermore, different patients with a spinal lesion in the same area can show variations in the clinical pattern of their condition.

There has been much discussion about the pathophysiology of the differences between spinal and supraspinal or cerebral spasticity. Although there are clinical differences, most of them can be understood by the level of the lesion of the UMN. Most of the important upper motor neurones controlling spinal reflex activity arise in the brain stem, but the ventromedial reticular formation, the origin of the main supraspinal inhibitory tract (dorsal reticulospinal pathway), is under cortical control. The motor areas of the cortex facilitate this area, augmenting the inhibitory drive down to the spinal cord. A lesion of these corticobulbar fibres, either in the cortex or in the internal capsule, withdraws cortical facilitation of the inhibitory pathway, leading to mildly reduced inhibitory drive and net excitation of spinal cord activity. The result is less severe positive-UMN features than a lesion

of the dorsal reticulospinal pathway. This explains why strokes or other supraspinal lesions produce some spasticity, hyper-reflexia, and possibly some clonus, but far less than that seen in a spinal cord lesion.

A partial spinal cord lesion, which totally destroyed the inhibitory pathways but preserved the excitatory fibres, would leave spinal activity uninhibited. The unopposed strong excitatory drive to the spinal reflexes would cause marked spasticity, hyper-reflexia and flexor and extensor spasms.

In the complete spinal cord lesion, which affects both inhibitory and excitatory pathways, spinal reflexes lose all supraspinal control and eventually become hyper-active.

So the clinical patterns of the UMN syndrome are largely determined by location of the lesion and can be divided into those three main areas; the cortex, the brain stem and the spinal cord. These patterns are also dependent upon the time after the lesion, which will be discussed at the end of this paper. Briefly, immediately after a lesion, there may be a period of shock, or depression of reflexes, which resolves and is replaced by hyper-reflexia.

Spinal reflexes

Returning to the pathophysiological categories, let us consider the spinal reflexes, since they are responsible for most of the positive features of the UMN syndrome. They can be broken down further into different categories. Firstly, there is disinhibition of existing normal reflexes, which are involved in walking and all other movements. One form is the propriospinal phasic stretch reflex, also known as deep tendon reflexes or tendon jerks. These become exaggerated and cause clonus, which is simply a version of a hyperactive phasic stretch reflex. Then there are nociceptive reflexes, which include the flexor withdrawal reflex. If you stand on a sharp object, a pin or a needle, there is an immediate dorsiflexion of the ankle, flexion of the hip, and flexion of the knee, to withdraw the leg from that stimulus. This is a normal reflex, but in the UMN syndrome, it becomes disinhibited and produces flexor spasms.

Secondly, there is the release of primitive reflexes, which exist at birth but are later suppressed during development, such as the Babinski sign and the positive support reaction. We are all familiar with the Babinski sign (cutaneous), but the positive support reaction is a proprioceptive spinal reflex. When the foot is placed against a solid surface there is a tendency for the leg to straighten, assisting standing. It is seen in babies, but is suppressed soon after birth.

Thirdly, and somewhat controversially, a new reflex appears to cause spasticity. At rest in a totally relaxed normal person, there is no detectable reflex activity in response to muscle stretch at the rates usually used in the clinic, when testing for tone. However, in the UMN syndrome, this tonic stretch reflex exists and is the cause of spasticity. So spasticity cannot be considered an exaggeration of a normal reflex, caused by disinhibition, as discussed in the first category.

So overall, there are the supraspinal fibres that provide inhibitory input into the spinal interneuronal network, controlling all the reflexes in the spinal cord. There are both negative and positive inputs controlling the reflexes, which can be divided into proprioceptive, cutaneous, and nociceptive reflexes. It is thus possible to divide the clinical phenomena into basic physiological categories associated with the spinal reflex phenomena that have been studied electrophysiologically.

Muscle tone

The concept of normal muscle tone is very important to understand. If a normal person is fully at rest, and a limb passively moved, muscle contraction contributes nothing to the resistance felt. If that person is relaxed enough, all the resistance is due to biomechanical factors – the elastic properties of tissues, joints, blood vessels, muscles, etc. Using an electromyograph (EMG), there is no EMG activity at the normal rates of muscle lengthening. Thus, there cannot really be hypotonia due to impairment of stretch reflexes. So-called hypotonic patients, especially in cerebellar syndromes, or floppy babies, do not really have a loss of muscle tone; they are just very, very relaxed or weak. It is highly likely that our idea of normal muscle tone, which we developed clinically, includes many people who are really not fully relaxed. Most, if not all, normal muscle tone is biomechanical. However, the idea of the pathological development of a neural component is quite important, because this is spasticity.

Spasticity

The definition of spasticity states that it is a form of hypertonia due to a velocity-dependent increase in tonic stretch reflexes, which results from abnormal spinal processing of proprioceptive input. This may not sound very familiar in terms of what is seen in clinical practice. We accept that it is a form of hypertonia, increased muscle tone, and know that it is velocity-dependent – the faster you do the stretch, the greater the resistance and the more reflex activity you get. We might even be aware that it is the result of a tonic stretch reflex, that is a sustained muscle stretch, rather than a quick one, as occurs with a tendon reflex. However, the key to understanding the basis of the problem is the abnormal processing of proprioceptive input in the spinal cord.

Passive stretches of the elbow flexors through a range of velocities in a normal subject at rest produce different patterns of EMG at the different rates of stretch. At 80° per second, there is no response from the muscle. If the rate is approximately doubled, the muscle still fails to react; there is no tonic stretch reflex present. It is not until extremely fast rates of stretch that a small response is seen, but at these rates it is almost a tendon reflex itself. This speed of stretch is nothing like that used in clinical practice to test tone.

In contrast, in a patient with spasticity there is a lot of muscle activity with stretch, even at the very slow rate of elbow extension. The muscle activity increases with the speed of the stretch with a fairly good linear relationship. When the stretch is performed slowly, tone may feel relatively normal, but if it is done more quickly, there is a clear resistance. This is the characteristic velocity-dependence of spasticity.

The reason why it is not correct to consider spasticity, or a tonic stretch reflex, a disinhibited normal reflex is that there is no reflex present at rest. For those who do consider it a hyperactive normal reflex, there is uncertainty about whether the hyperactivity is due to lowered or increased threshold.

The key points about spasticity are that it is:

- a tonic stretch reflex (tonic meaning sustained in this case);
- mediated by Ia afferents, predominantly in the muscle spindle. Passive stretch of the muscle excites the muscle spindle, sending sensory input back to the spinal cord through largely monosynaptic, but also oligo- and poly-synaptic reflexes, which in turn send an efferent impulse to the muscle, causing it to contract;
- velocity-dependent;
- dynamic – in the classical definition of spasticity, if after stretching you stop moving and hold it stretched, then the muscle should stop contracting. However, in many cases if the stretch is maintained, the stretch reflex continues and the muscle still keeps contracting, at least for a time. So, although spasticity is considered classically dynamic, there is also a static component;
- length-dependent – the excitability of the tonic stretch reflex depends upon the length of the muscle at which it is stretched.

An important point about spasticity is the way in which the tonic stretch reflex has become hyperexcitable. Initially, it was thought that the muscle spindles had become more sensitive, and when stretched would produce a greater discharge, resulting in a larger impulse to the spinal cord, and greater corresponding reflex output, causing a greater muscle contraction. However, this has been shown not to be true. The muscle spindles are no more sensitive in a spastic patient than they are in a normal person. The same amount of stretch produces the same amount of spindle activity feeding back to the spinal cord. It is what goes on in the spinal cord that has changed. The central excitability is increased; the reflex is enhanced within the spinal cord. It is not true to say that spasticity is a peripheral phenomenon – it is very clearly a spinal phenomenon.

Flexor spasms

Flexor spasms are extremely common, but the pathophysiology underlying them is quite different from that underlying spasticity. They are pathophysiologically quite independent of spasticity, deep tendon hyperreflexia and clonus. This is because flexor spasms are not due to abnormal proprioceptive reflexes. Flexor spasms are simply disinhibited normal flexor withdrawal reflexes, as in the example of standing barefoot on a pin.

In the patient with the UMN syndrome, either the threshold for the flexor withdrawal reflex is lowered, or the gain of the system is raised, or quite possibly a little of both. A group of afferents that come from the periphery, from the skin, the muscle, subcutaneous tissues, the joints, collectively called flexor reflex afferents, mediate these polysynaptic flexor reflexes. They are so-named because when activated cause contraction of the flexor muscles, but also inhibition of the extensors. This is an example of a normal spinal reflex that has become hyperexcitable, or disinhibited. The supraspinal pathways mentioned earlier, both excitatory and inhibitory, actually inhibit flexor reflex afferents, although the inhibitory dorsal reticulospinal tract is the most important. In the event of a total cord transection, all the supraspinal inhibitory influences are lost, resulting in intense flexor spasms.

The clasp knife phenomenon

The clasp knife phenomenon is a combination of the tonic stretch reflex underlying spasticity, modified by flexor reflex afferents. In this situation, if you are bending a patient's knee, for example, you will encounter resistance due to spasticity, because you are stretching the quadriceps. As you keep going, it reaches a point at which the resistance disappears. This results from a combination of two things. Firstly, the spasticity is not only velocity-dependent, but it is also length-dependent; in the quadriceps, the tonic stretch reflex is greater when the muscle is short, than when it is long. As you bend the knee, the quadriceps lengthens, thus reducing the excitability of the tonic stretch reflex. At the same time, the resistance to the stretch slows the movement, reducing the spasticity by virtue of its

velocity-dependence. So, this combination of velocity and length-dependence leads to a point where the stretch is so slow and the muscle length so long, that the excitability of the tonic stretch reflex is subthreshold and the resistance melts away.

At one time this clasp knife phenomenon was thought to be due to Golgi tendon inhibition via 1B neurones. However, this is now known not to be true.

Efferent drive

Returning to the positive UMN signs, we will now briefly consider efferent drive. These are continuous muscle contractions that occur, in the apparent absence of voluntary contraction and of any sensory feedback from the periphery (proprioceptive, cutaneous or nociceptive). This was studied by Denny-Brown (1980), who noticed that some of his spinal cats assumed a sustained flexed position. He called this spastic dystonia. There was however, no voluntary activity in this posture and no actual stretch of the muscle, as in a tonic stretch reflex, they just seemed to want to be that way. When he cut the dorsal root, this position persisted.

Unlike spasticity, or tendon hyper-reflexia, it was not entirely dependent upon sensory feedback from the periphery; that is, it was not afferent-mediated but rather efferent-mediated. It appeared to come from a tonic supraspinal drive to the alpha motor neurones, although the underlying cause remains unclear. One example in humans is the hemiplegic posture; the patient who stands or walks with sustained contraction of the elbow, wrist and fingers flexors, and extension in the leg. This is not due to a voluntary movement, nor to a reflex action, as far as can be determined, and may therefore be considered to be spastic dystonia.

Associated reactions

We are all familiar with the stroke patient in whom their hemiplegic elbow becomes progressively more flexed as they walk. This is not a voluntary movement and does not appear to be due to any stretch or nociceptive reflex. It seems to be due to tonic efferent drive to the alpha motor neurones of the elbow flexors, a form of spastic dystonia. The amount of flexion appears to be related to the amount of effort being expended elsewhere. In patients with extreme difficulty walking, the elbow flexion is greater. As their walking improves, so often does this associated reaction, despite their having had no specific treatment to try and suppress it.

Associated reactions are a remote form of synkinesis and may be due to a failure to inhibit spread of motor activity. This spread might occur through propriospinal pathways in the spinal cord. It is an interesting phenomenon, because of the high correlation with the motor effort expended elsewhere. It also correlates partially with the amount of spasticity that is present in the limb itself.

Disordered control

The third major pathophysiological category of the positive features of the UMN syndrome is disordered control of voluntary movement. In particular, co-contraction. Co-contraction is the simultaneous contraction of agonist and antagonist muscle groups, for example, the wrist flexors and extensors.

Many years ago, Sherrington (1906) described the principle of reciprocal innervation, controlling agonists and antagonists. For example, if you want to flex your wrist, you must inhibit the muscles that would tend to oppose that, the extensors. This is called reciprocal-inhibition. However, there are occasions when we want co-contraction, such as trying to hit a tennis ball, when it is important to have a strong, rigid wrist – this is normal co-contraction. When needed, co-contraction results from controlling reciprocal inhibition. So, co-contraction can be functional, but in the UMN syndrome it becomes uncontrolled and interferes with normal movement – this is pathological co-contraction.

Control of reciprocal inhibition occurs at both the cortical and spinal levels. In the UMN syndrome, reciprocal inhibition is disordered in two ways. The first is through reduced reciprocal inhibition, leading to inappropriate or pathological co-contraction. Normally, while extending the elbow, the extensors inhibit the elbow flexors to allow the movement. In the UMN syndrome, the elbow flexors are not inhibited and oppose the movement. The elbow flexor activity is a combination of a tonic stretch reflex (elbow extension stretches the flexors) and simultaneous UMN activation of the elbow flexors and the extensors.

Sometimes reciprocal inhibition is so disordered that the intended movement is over-shadowed by the action of the stronger antagonists. I saw one case where the patient was asked to dorsiflex their ankle. As they tried, there was a small amount of EMG activity in the dorsiflexors, but soon the plantar flexors were activated, through a loss of reciprocal inhibition, and the foot actually plantarflexed – the opposite of the intended movement. This is also seen in the upper limbs. When a patient is asked to open their fingers, they actually close more, even though they are trying to open them.

The second form of disordered reciprocal inhibition is excessive reciprocal inhibition, which can produce the appearance of weakness. An example of this is excessive

inhibition of the tibialis anterior by the gastrocnemius-soleus group. If the gastrocnemius-soleus muscles are contracted voluntarily, through reflex activity, co-contraction or spastic dystonia, the dorsiflexors will be strongly (reciprocally) inhibited. The dorsiflexors may already be weak from the stroke and, through reciprocal inhibition, seem even weaker. If you stop the plantar flexors from being so overactive, it is possible to uncover some strength in the ankle dorsiflexors that was previously not apparent.

In addition to co-contraction, biomechanical factors might contribute to difficulty with movement. This is common around the ankle, where soft tissue changes in the gastrocnemius-soleus group makes the muscles and tissues tight impairing passive and active dorsiflexion of the ankle. It is important to recognize the two components, since it will affect the therapy required.

Overview of mechanisms

How does the UMN lesion cause all these problems? The majority of the problems result from a loss of control of the spinal reflexes. Spinal reflex activity is normally tightly regulated and if inhibitory control is lost, the balance is tipped in favour of excitation, resulting in hyperexcitability of the spinal reflexes.

If it were a simple case of imbalance, the spinal reflexes would become hyperactive very quickly after the UMN lesion. However, frequently the opposite occurs in the early stages, say, after a stroke and there is depression of spinal reflexes. In fact, with complete spinal cord transection, the suppression is profound with no reflexes for a long time, the stage of spinal shock. This can occur following both spinal and supraspinal causes of the UMN syndrome. The delay in onset of hyperreflexia after a lesion is highly variable and is delayed the longest in humans. It appears that the smaller the animal, the shorter the period of shock.

The fact that there is a period of shock, followed by a transition period when reflexes return, but are not hyperactive, suggests that this is not just simply a question of switching off supraspinal inhibition, or altering the balance. It implies that there must be some sort of rearrangement, a kind of neuronal plasticity, occurring within the spinal cord, and most probably at the cerebral level as well. One possibility is sprouting of afferent axons. Afferent fibres might sprout, attach to previously inhibitory synapses, and convert them to excitatory synapses.

Alternatively, there could be changes in receptor sensitivity. The concept of denervation hypersensitivity within the nervous system is well known. It does not occur immediately and is due to the up-regulation or possibly proliferation of receptors. Denervation hypersensitivity might be well known, but the idea of co-axial sprouting was not given much credence until recently. It is now fairly clear from several spinal experiments in cats, that collateral sprouting of afferents does occur within the central nervous system.

Once we understand the neuronal mechanism underlying the change in spinal reflex excitability it might be possible to interfere with it leading the way to new therapies.

Biomechanical changes

We have considered the importance of the UMN syndrome in producing various types of muscle overactivity, which can cause hypertonia, a reduced range of movement, and ultimately impaired function.

However, the effects of weakness and biomechanical changes should not be overlooked. Weakness leads to immobilisation of the muscle at short length, and so do spasticity and the other forms of muscle overactivity. When shortened for a prolonged time, secondary biomechanical changes occur within the muscle and other tissues, which lead to stiffness and hypertonia. Sometimes they lead to contracture. Both stiffness and contracture cause a reduced range of movement, and impair function.

Summary

Although the positive and negative features of the UMN syndrome have different pathophysiology, they

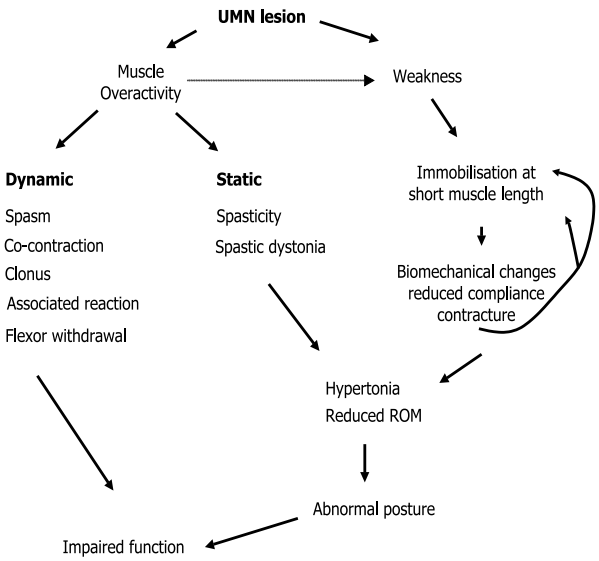

Figure 2 An overview of the features of the upper motor neurone lesion. This overview tries to integrate the positive and negative features of the upper motor neurone lesion, including biomechanical changes.

conjointly cause hypertonia, reduced range of movement and impairment of function (Figure 2). Understanding that these two processes can occur independently, but sometimes in an overlapping way, helps in the approach to treatment. Clearly, where hypertonia is due to soft tissue changes, the antispasticity drugs baclofen, diazepam, and tizanidine, are not going to be very helpful. For muscle overactivity, medical treatment to reduce the excitability of the nerve pathways, and focal chemodenervation, are very important.

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