Connecting the dots: Musculoskeletal adaptation in cerebral palsy

de Bruin, Marije

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Chapter 2

Why is joint range of motion limited in cerebral palsy patients?

M de Bruin, MJC Smeulders, M Kreulen

Abstract

Patients with spastic cerebral palsy of the upper limb typically present with various problems including an impaired range of motion that affects the positioning of the upper extremity. This impaired range of motion often develops into “contractures” that further limit functioning of the spastic hand and arm. Understanding why these “contractures” develop in cerebral palsy will affect the selection of patients suitable for surgical treatment as well as the choice for specific surgical procedures. The generally accepted hypothesis in patients with spastic cerebral palsy is that the hyper-excitability of the stretch reflex combined with an increased muscle tone result in extreme angles of the involved joints at rest. Ultimately, these extreme joint angles are thought to result in fixed joint postures. There is no consensus in the literature concerning the pathophysiology of this process. Several hypotheses associated with inactivity and overactivity have been tested by examining the secondary changes in spastic muscle and its surrounding tissue. All hypotheses implicate different secondary changes that consequently require different clinical approaches. In this review, the different hypotheses concerning the development of limited joint range of motion in cerebral palsy are discussed in relation to their secondary changes on the musculoskeletal system.
Introduction

Spastic cerebral palsy is primarily a neurological condition characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks resulting from hyper-excitability of the stretch reflex (Lance, 1980). However, most patients present with deformities and limited ranges of motion of the extremities rather than with tendon jerks. As a general understanding, such movement limitations are supposed to be caused by secondary changes to muscles and soft tissues. Successful treatment of limited joint range of motion, known as contracture, in patients with spastic cerebral palsy (sCP) has been achieved by splinting, botulin toxin injection, surgical lengthening, or tenotomy of spastic muscles. This suggests that the muscles are the origin of the clinical problem (De Roode et al., 2010). Long standing loss of movement might lead to changes in the joint capsule and ligaments. This adds to the contracture but is not regarded as its primary cause and thus not the focus of this review.

Despite extensive research on the neuropathophysiology of movement disorders in sCP, there is no general agreement whether and how this leads to secondary muscle adaptations yielding a limited range of joint motion (Filloux, 1996). Even when spasticity had been successfully eliminated for more than ten years after dorsal rhizotomy, limitations in range of motion have been reported to continue to progress (Tedroff et al., 2011). This suggests that the observed movement limitations may not be primarily caused by an adaptive response alone. Therefore, we choose not to use the term “contracture” until the origin of the movement limitations in spastic cerebral palsy is clarified.

In this review we address the questions as to how movement limitations develop in these patients, and what secondary changes to muscles occur? This knowledge may affect the selection of patients suitable for surgical treatment as well as the selection of specific interventions.

Methods

We performed an extensive literature search for fundamental studies that address the pathophysiological mechanisms that are thought to influence joint range of motion in sCP. Clinical outcome studies and animal experiments were not included in
our review. Clinical outcome studies do not directly address the pathophysiological origin of limited motion in these patients. Animal experiments are not included because extrapolation of data from animal to human muscle is difficult to justify. Animal muscles behave differently because of differences in morphology, function, and adaptive capabilities. Moreover, a valid animal model for muscle spasticity does not exist (Wright & Rang, 1990).

The suggested mechanisms to explain limited motion in human cerebral palsy studies can be divided into three main groups that will be discussed in this review: 1) histology and histochemistry (i.e. cell characteristics, myofibre typing and diameter, connective tissue content and gene expression); 2) morphology/geometry (i.e. muscle and myofibre length, pennation angles, sarcomere number and length); and 3) mechanics (i.e. force generation, tension and moments).

**Histology and histochemistry**

Although histological examination is relatively easy to perform, only a limited number of muscle cells can be analysed. Therefore, the observations in muscle samples may not be representative for the whole muscle. Moreover, while histological analysis may show the presence of morphological changes, it does not explain the consequences or significance of these changes to functional properties such as stiffness.

Many efforts have been made to provide evidence for the development of structural changes of spastic muscles as an adaptive response to pathological conditions. Generally, atrophy is seen as a consequence of disuse and hypertrophy as an adaptive response to overactivity. In spasticity atrophy and hypertrophy as well as unchanged fibre diameters with or without fibrosis have been reported (Castle et al., 1979; Romanini et al., 1989; Rose et al., 1994; Ito et al., 1996; Booth et al., 2001; Marbini et al., 2002; Lieber et al., 2004; Pontén et al., 2005; Pontén & Stål, 2007). The longstanding limited ranges of joint motion have been proposed to lead to structural shortening of intra- and extramuscular connective tissues, muscle fibres, or joint capsules (Castle et al., 1979; Booth et al., 2001). However, controversy exists as most histological studies have failed to prove that spastic muscles are fibrotic and structurally shortened. Just one report has found a significant correlation between
Clinically measured muscle tone and the amount of collagen in spastic muscle biopsies (Booth et al., 2001), while several other reports have shown biopsies of spastic muscle containing normal amounts of connective tissue (Romanini et al., 1989; Ito et al., 1996; Marbini et al., 2002). Even more illustrative for this contradiction are reports of an increased connective tissue in some biopsies from several spastic muscles and not in others within the same study (Rose et al., 1994; Friden & Lieber, 2003). Fifty percent of muscle biopsies were considered normal or showed only limited abnormality in those studies, despite “the presence of static and dynamic contractures” involving the target muscles. Moreover in a recent study the connective tissue content of the hamstring muscles and degree of limitation of knee movement were reported not to be correlated (Smith et al., 2011). Our group also conducted a study and found differences between morphological aspects of the connective tissue structures between spastic and control flexor carpi ulnaris (FCU) muscles. FCU muscle in sCP patients had thickened connective tissue tracts surrounding the intramuscular vessels and nerves, while there was no difference in connective tissue structures at other locations within the FCU muscle (unpublished observations). The thickening and presumed stiffening of these connective tissue tracts suggest that spasticity causes relatively greater loading of these structures. From a different perspective, the giant protein titin is regarded to be responsible for intracellular stiffness affecting the passive tension in whole muscle and myofibres (Magid & Law, 1985; Linke et al., 1996; Gajdosik, 2001). Contradictory to this, Smith et al. (Smith et al., 2011) found more titin in spastic fascicles but no difference in tension between control and spastic fascicles. Apparently, the relationship between titin and passive muscle tension is not clear. Recently, altered gene expression in tendons of spastic muscle (Gagliano et al., 2009) as well as transcriptional upregulations have been hypothesized to alter, amongst other factors, extracellular matrix components (Smith et al., 2009). However, these transcriptional differences were found in both flexor and extensor muscles within the spastic arm. This indicates that both wrist flexors and extensors have similar adaptation to sCP (Smith et al., 2009) yet the clinical picture of extreme wrist flexion would suggest that wrist flexors would be affected differently to wrist extensors. From this evidence we conclude that there is no current evidence for muscle
adaptations on a histological or histochemical level being responsible for the formation of movement limitations in sCP.

**Morphology / geometry**

Muscle morphology is defined by several factors i.e. volume, fascicle length, tendon properties and the pennation angle of the muscle fibres to the aponeurosis (Fry et al., 2004; Fry et al., 2007; Malaiya et al., 2007; Mohagheghi et al., 2007; Wren et al., 2010). These factors contribute to the mechanical characteristics of a muscle. The properties of muscle morphology have been measured directly during surgery (Lieber & Friden, 1997; Pontén et al., 2007; Smith et al., 2011), but ultrasonography is an easier and non-invasive way to measure muscle morphology in vivo. Given the 3D architecture of fascicles in muscle, 3D ultrasound is preferred over 2D ultrasound to prevent over- or underestimation of geometrical parameters (Bénard et al., 2009). The pennation angle, muscle belly length, and muscle fascicle length determine how much a muscle can lengthen and shorten i.e. muscle excursion (Van der Linden et al., 1998). Pennation angle has been shown not to change with growth of the gastrocnemius muscle in healthy subjects (Bénard et al., 2011) and not to differ significantly between spastic gastrocnemius muscles and healthy ones (Shortland et al., 2002; Malaiya et al., 2007). Yet the spastic medial gastrocnemius muscle belly has been estimated to be shorter compared to that of healthy subjects, which has been attributed to a reduction of fascicle length (Mohagheghi et al., 2008; Wren et al., 2010) or reduction in cross-sectional area of the fascicles (Heslinga et al., 1995; Huijing & Jaspers, 2005). However, as noted by the authors, the activity of the spastic muscles may have confounded the measurements, as muscle shortness may have been a result of muscle activation, rather than of structural changes to the muscle (Mohagheghi et al., 2008; Wren et al., 2010).

To date, intraoperative measurements have failed to bring agreement on the specific changes that cause reduction of fascicle length and consequently shortening of the spastic muscle (Lieber & Friden, 2002; Smeulders et al., 2004b; Pontén et al., 2007). Laser diffraction measurements during surgery of spastic arm muscles showed that sarcomeres were stretched more at certain wrist angles compared with sarcomere lengths in patients with a radial nerve palsy (Pontén et al., 2007). Furthermore,
spastic muscle has been reported to operate at higher sarcomere lengths (Lieber & Friden, 2002; Smith et al., 2011). This was hypothesized to be a result of a reduced longitudinal growth of myofibres in sCP. However, it is accepted increasingly that loss of serial sarcomeres within muscle fibres as a cause for structural shortening of muscle is not a common finding in spastic muscles, with muscle atrophy present in some, but not all (Smeulders et al., 2004b).

**Mechanics**

The suggestion that muscle adapts to spastic neural input by loss of sarcomeres in-series evolved from famous experiments by Tardieu, Tabary and co-workers (Tardieu et al., 1982a; Tardieu et al., 1982c; Tardieu & Tardieu, 1987). Patients with spasticity were subjected to in vivo mechanical testing. The authors showed that passive ankle movement in sCP provoked higher mechanical resistance than in healthy controls (Tardieu et al., 1982a; Tardieu et al., 1982c; Tardieu & Tardieu, 1987). These observations led to numerous studies of in vivo assessment of mechanical resistance to movement of spastic human joints. But estimating actual muscle force from in vivo resistive moment data has extremely limited accuracy because only the net joint moment, rather than the actual force that a muscle exerts at a joint can be assessed. This moment not only depends on the force exerted, but also on the moment arm. The moment arm varies among subjects and is difficult to assess accurately. In addition, the net moment exerted at a joint represents the net moment of many muscles and passive structures and it is impossible to distinguish accurately the force contribution of a particular muscle. Furthermore, the increased mechanical resistance may be a reflection of shortening of the muscle-tendon complex by atrophy of the pennate muscle or a shorter or stiffer tendon. Each would lead to an increase in the stretch of a muscle per degree of joint angle change.

Several reports have discussed the influence of the resistance to stretch of human spastic limbs on the presence of a limited range of motion (Hufschmidt & Mauritz, 1985; Sinkjaer & Magnussen, 1994; Becher et al., 1998; Lebiedowska & Fisk, 1999; Vattanasilp & Ada, 1999; Lamontagne et al., 2000; Vattanasilp et al., 2000; Mirbagheri et al., 2001). These reports studied mainly the lower limbs in patients with sCP. Lamontagne et al. (Lamontagne et al., 2000) concluded that the resistance
to passive stretch was increased in the spastic muscle of some of their patients. The absence of EMG activity during these measurements ruled out stretch reflex activity as a cause for this increased resistance. In other patients of the same group, however, they found the resistance to stretch to be less than in healthy control subjects. Furthermore, there was only a moderate correlation between the resistance to stretch and the limitation of the range of motion of the involved joint. A similar study showed that the spastic ankle had an increased resistance to stretch without a difference in stretch reflex in spastic patients as compared to healthy subjects (Sinkjaer & Magnussen, 1994). However, the increased resistance did not correlate to the decrease in ankle range of motion in the patient group. Instead, resistance to stretch depended significantly on muscle activation, with higher activation leading to higher resistance. From the above and based on our experience we believe that an increased passive stiffness due to structural muscle adaptation should not depend on the activation level of the muscle.

Several studies that focused on resistive moments have failed to correlate resistance to stretch around the joint to limited range of motion (Becher et al., 1998; Lebiedowska & Fisk, 1999; Vattanasilp & Ada, 1999; Vattanasilp et al., 2000; Mirbagheri et al., 2001). Based on these reports on mechanical testing of spastic muscle, we conclude that: (1) although spastic muscles may clinically feel ‘stiffer’, this does not seem to result in increased resistance to passive stretching; and (2) proof of a correlation between increased resistance to stretch and limited range of motion of a joint is lacking.

Renewed interest in this field has led to analysis of spastic human muscle tissue mechanics (Friden & Lieber, 2003; Lieber et al., 2003; Smeulders et al., 2005; Smith et al., 2011). Initially, isolated spastic muscle fibre segments from different muscles of patients with cerebral palsy were stretched and passive tension was measured in these fibre segments. This tension was compared to the tension in fibre segments from healthy muscle (Friden & Lieber, 2003). They found that tension in the spastic fibre segments was significantly higher than in healthy muscle fibres, indicating that the stiffness of the spastic muscle fibres was increased. Subsequently, the same authors studied the tension of small bundles of fibre segments including the extracellular connective tissues, rather than that of single fibres and reported that
the bundles of spastic muscle fibres were actually less stiff compared to non-spastic muscle fibre bundles (Lieber et al., 2003). Contradictory to this are the results of a controlled study that compared tension of both isolated fibres and small fibre bundles of the same muscle in sCP patients with healthy subjects (Smith et al., 2011). Tension of the sCP small fibre bundles increased faster than tension of the control bundles at increasing degrees of stretch, while there were no differences in tension of the isolated fibres. Moreover, there was no relation between the severity of limitation in range of motion of the knee and the measured passive tension.

In a study of patients with a spastic flexion and ulnar deviation deformity of the wrist, the mechanical properties of the FCU muscle were evaluated intraoperatively. FCU is assumed to be largely responsible for this joint mal-positioning, but the muscle appeared to be around the optimum sarcomere length for force generation with low passive forces at maximum extension of the wrist (Smeulders et al., 2004a). This implies abundant overlap, rather than overstretching of the sarcomeres and neither muscle atrophy, nor a loss of in-series sarcomeres seemed to have caused the limited range of motion of the wrist in these patients. Unfortunately, the study design did not allow for comparison to the characteristics of non-spastic FCU muscle. However, the passive and active length-force properties of the partially isolated spastic FCU were similar to those predicted for healthy muscle (Lieber & Friden, 1997; Burkholder & Lieber, 2001; Smeulders et al., 2004a), indicating that length-force characteristics of the spastic FCU (released from its environment) may not be dramatically different from a non-spastic one.

Conclusion

It has always been comfortable to relate the presence of a clinical “feel” of stiffness to adaptive local responses of muscle and connective tissue. Alternatively an imbalance between agonistic and antagonistic muscle groups is often regarded as the cause of the movement limitations. Even with a lack of sound scientific proof, these ideas are still commonly acknowledged and used as the basis of treatment protocols. Part of the contradictions that are present in the literature may be explained by the many different approaches to study the alleged muscle adaptations
and their relation to limited joint motion. Additionally, unexplainable results have often been attributed to factors that were not studied.

The analysis and interpretation of all different contributors to muscle function is very complex. This review covers the extensive field of muscle function studies. We admit to having simplified the discussion of some muscle parameters for the purpose of this overview. Nonetheless the scientific work on spastic muscle function reveals a lack of a sound scientific consensus regarding the nature of the contribution of spastic muscles to the disabling joint positions of the extremities in spastic paresis.

From this we can conclude that movement limitation in sCP patients cannot be attributed to one single mechanism. Rather, a combination of changes in muscular control and connective tissue could result in the characteristic posture that is seen in sCP limbs. Therefore, we caution against treatment of limitations of movement in these patients as if these were based on structural muscle contractures.