IC 25: The End Organ: Muscle in the Cerebral Palsies

Intervention to muscles in children with cerebral palsy - do we need gardeners rather than carpenters?
Martin Gough

Introduction
Intervention to lengthen the musculotendinous unit, or to reduce its activity, are commonly performed in children with cerebral palsy (CP) with joint passive range being used as a surrogate outcome measure of musculotendinous unit length. The development of muscle deformity in children with CP is often attributed to spasticity, which has been defined variably as a velocity-dependent resistance to stretch or a persisting increase in muscle tone. Stretch of skeletal muscle is thought to be needed to encourage muscle growth: spasticity, by impairing the ability of a muscle to be stretched, is thus considered to lead to a failure of appropriate muscle growth and the consequent development of deformity. Nonoperative intervention to lengthen muscle generally involves the use of muscle stretch, either applied for short periods or over a prolonged period, with the aim of preventing muscle deformity and facilitating muscle growth by the addition of sarcomeres to muscle fibres. Short stretches are applied through stretching programmes, while more prolonged stretches are applied through the use of serial casting or orthoses. Spasticity is addressed by denervation of muscle using botulinum toxin, with the aim of improving the capacity of a muscle to respond to passive stretch and in this way to facilitate muscle growth and function. Consensus statements have recommended the use of continuous passive stretch for children with CP from the age of six months (Gericke 2006) and the use of repeat intramuscular botulinum toxin injection from the age of two years (Heinen 2010). Nonoperative intervention, in the form of stretching modalities or botulinum toxin, is generally used with the aims of maintaining muscle growth or at least of deferring muscle growth until a single surgical intervention can be performed as the child nears skeletal maturity. Surgical intervention is generally considered to be potentially destructive to muscle and is not usually considered as an initial intervention in younger children.

The previous speakers have discussed the complex alterations in skeletal muscle in children with cerebral palsy both in terms of the altered physiology and compliance of the muscle fibre and the extracellular matrix, and also in terms of overall muscle morphology and development: in turn, it seems appropriate to consider whether our present model of the development of deformity in children with cerebral palsy appropriately captures the complexity of the subject and whether a further evolution of the underlying model and of our therapeutic approach could be considered.
Muscle deformity in cerebral palsy
Muscles in children with CP have impaired development with reduced muscle volume and an increase in passive stiffness from an early age. Barber et al (2011), using ultrasound scanning, noted a reduction in medial gastrocnemius volume, physiological cross-sectional area and muscle fascicle length in children with spastic cerebral palsy aged between 2 and 5 years. Willerslev-Olsen et al (2013) noted increased passive stiffness in the calf musculotendinous unit complex in children with CP at the age of 3 years which was related to intrinsic changes in the muscle rather than to an alteration in muscle innervation or an altered neurological response to stretch. A similar pattern of increased stiffness in the gastrocnemius muscle in children with CP was noted by Alhusaini et al (2010): this group also noted (2011) that the stiffness appeared intrinsic to the muscle and was not related to activation of the muscle in that it was not altered when the muscle was denervated by botulinum toxin. The cause of the reduction in muscle size in children with CP may relate to a combination of impaired growth because of altered muscle innervation and an altered pattern of loading, with a resulting altered balance in the muscle between muscle fibre growth and muscle connective tissue growth (Gough and Shortland, 2012). The reduced muscle volume is associated with a reduction in muscle strength which will be exacerbated by the reduced capacity of the child with CP to maximally activate their muscles (Stackhouse et al 2005).

Muscle is a very plastic tissue: the muscle activation pattern, the pattern of mechanical loading, the energy substrates available and the presence of circulating growth factors influence gene expression within the muscle which in turn defines the muscle fibre type, the ability of the muscle to generate energy for function, and the balance between contractile and non contractile components. There are competing protein synthesis and degradation systems within muscle which also influence muscle growth and function as shown in the diagram below: muscle in children with CP retains this plasticity and can respond positively or negatively to intervention.

This model gives a useful framework with which to consider the potential benefits and risks of intervention: these are outlined below.
**Stretching**

Passive muscle stretch has not been shown to correct deformity or promote muscle growth whether used as part of a therapy programme (Butler 2001, Pin 2006), through the use of orthoses (Morris 2002) or through serial casting (Blackmore 2007). A recent Cochrane review (Katalinic 2010) concluded that in people with neurological conditions, there was moderate to high quality evidence to indicate that passive stretch does not have clinically important immediate, short-term or long-term effects on joint mobility.

These findings are not entirely surprising. Stretch without contraction in the human gastrocnemius does not appear to lead to protein synthesis (Fowles 2000), and cultured muscle cells show a prolonged inhibition of protein synthesis after mechanical stretch without activation (Atherton 2009). Rather than resulting in muscle growth, repeated passive stretch instead appears to promote expression of the atrophy pathway in the rat soleus (Gomes 2006). Van Dyke et al (2012) recently showed that passive stretch of the adult rat soleus following tenotomy did not alter the rate of sarcomere loss in comparison to unstretched tenotomised muscle: sarcomere loss was reduced but not prevented when stretch was combined with electrical stimulation of the muscle. Even if stretch of muscle did promote sarcomerogenesis, this would have a limited benefit in terms of muscle belly length because of the limited contribution of muscle fibre length to musculotendinous unit length (Benard 2011). It must also be noted that a stretch applied to growing muscle may have a greater effect on the tendon than on the muscle belly and this effect is likely to be short-lived (McNee et al 2006, Blackmore et al 2007). Overall, immobilisation of muscle leads to a rapid reduction in protein synthesis and an increase in protein degradation, together with a reduction in the oxidative capacity of the muscle leading to atrophy and a reduction in function.

Orthoses are commonly used to provide a stretch and to promote function: their use will need to balance the potential benefits and risks of immobilization as For example, the use of ankle-foot orthoses may confer enough stability to allow a child to stand and take steps to offset the potential adverse effects of the orthoses in terms of muscle growth. The use of night-time splinting, however, would be difficult to support in terms of the facilitation of muscle growth.

**Botulinum toxin**

Botulinum toxin use in adult animal muscles has been reported to cause marked atrophy. An adverse effect of an intervention on growing muscle may result in a permanent deficit in muscle size or volume: the use of botulinum toxin in 29 day old rats resulted in marked atrophy and an impairment of muscle growth that did not respond to subsequent exercise (Velders 2008). Tedroff et al (2009) reviewed the outcome in children with cerebral palsy treated with botulinum toxin for spasticity or limitation of joint motion and noted a progressive reduction in joint passive ranges, following an initial improvement. They concluded that
botulinum toxin was not effective in preventing muscle deformity and suggested that it may instead promote the development of deformity.

There have been some recent studies looking at the outcome of botulinum toxin injection on muscle volume in children with CP. Williams et al (2013) looked at the effect of injection on the medial gastrocnemius of children with CP at 5 weeks following injection and noted only very mild reduction in muscle volume. Barber et al (2013), in contrast, noted a marked reduction in medial gastrocnemius muscle growth in children with CP following botulinum toxin injection compared to their typically developing peers whether they had one course or three courses of botulinum toxin injection. Van Campenhout et al (2013) noted significant atrophy in the psoas muscles of children with CP 6 months after injection. The apparent discrepancy between these studies may be explained by the difference in pre-trial exposure to botulinum toxin: all of the children in the study by Williams et al had previous botulinum toxin injection, while the children in the other studies did not. Botulinum toxin may have a greater effect when used for the first time as it appears to particularly target larger and more active muscles (Shortland et al, unpublished). A recent study by Mukund et al (2014) on the effect of botulinum toxin on healthy adult animal muscle noted an increase in expression of slow and immature isoforms, activation of genes in competing pathways of repair and atrophy, impaired mitochondrial biogenesis, and increased metal ion imbalance in the muscle cell. We have seen earlier that gene expression in skeletal muscle is altered and somewhat confused: it is not clear whether skeletal muscle in children with CP has the potential to recover completely from botulinum toxin injection.

Surgery
Surgical intervention is commonly viewed as destructive to muscle and is deferred as long as possible or avoided. Surgery can alter musculotendinous unit passive length, but also results in acute weakness of the muscle whether an aponeurotomy or tendon lengthening is performed (Jaspers 2002). Aponeurotomy is generally preferred where possible, but can result in significant weakness (Jaspers 2002) and increased compliance of the aponeurosis for up to 2 years afterwards (Jaspers 2005). Surgery does have the potential to increase muscle volume, as noted in the medial gastrocnemius following gastrocnemius recession (Fry et al 2007). This may be related to a reduction in the degree of eccentric loading of the muscle: eccentric loading may be related to persistent low-level injury which will promote the development of connective tissue rather than contractile tissue within the muscle.

Single-event multilevel lower limb surgery is recommended as a means of addressing all lower limb deformities at one sitting and in this way maximising the benefit of surgery and minimising hospitalisation for the child involved. It does not, however, address the limitations imposed on mobility by altered muscle control, muscle weakness, or reduced proprioception and the extent of surgery,
and the functional goals, will be influenced by the level of deformity and level of involvement of each child.

**Muscle strengthening**

Strengthening can improve muscle volume in children with CP but this may not be associated with an improvement in function (McNee et al 2009). The potential benefit of strengthening may be influenced by the level of selective motor control, by pre-existing deformity, or by the degree of commitment of an individual child to a strengthening programme.

**Summary and Conclusion**

On balance, the nonoperative intervention options available at the level of the muscle for a child with CP, with the exception of strengthening, would appear to carry a greater risk of contributing to the underlying growth impairment than of reducing it. Our increasing understanding of the plasticity of developing muscle and the role of muscle use and movement in CNS development raise exciting potential prospects for intervention. An early focus on enhancing muscle growth and function may benefit both muscle growth and metabolic capacity, and in this way reduce the incidence of musculoskeletal deformity and improve muscle endurance and function in the longterm. It may also provide a portal through which the development of the central nervous system may be influenced. Early intervention also offers the possibility of reducing or preventing the subsequent abnormal adaptive changes in muscle and in this way promoting subsequent muscle growth. How should we proceed?

The answer may be to shift our focus from the passive aspects of skeletal muscle, in particular our focus on muscle length, to a focus on muscle function and growth in terms of strength and oxidative capacity. This would mean a move away from a model centred on the concept of spasticity to one centred on muscle plasticity and capacity for growth. It would mean being judicious about the use of any intervention which could contribute adversely to muscle growth, and considering possible interventions such as early surgery which could reduce the abnormal loading of the muscle and in this way promote the development of contractile tissue rather than structural non contractile tissue. It would mean an increased focus on the basic science of muscle growth and function and increased collaboration with our colleagues in these fields with a view to developing new interventions which focus on improving muscle function rather than simply increasing musculotendinous unit length.

In summary, it would mean an increased understanding of the vulnerability and the potential for growth in skeletal muscle in children with cerebral palsy: perhaps a shift from being carpenters to gardeners?