



Commentary

Diagnosis and Treatment of Spasticity and Stiff Muscles



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Central nervous system (CNS) diseases such as cerebral palsy (CP), stroke (CVA), spinal cord injury (SCI) or multiple sclerosis (MS) often engender impaired motor control that might affect the performance of activities, to a level that requires intervention to improve the quality of life for the patient. However, the heterogeneity of consequences of the CNS disease and the complex nature of motor control makes it hard to precisely identify the underlying impairments for each patient. Additionally, effectively treating these chronic patients is limited by an absence of proper treatment options for many of these underlying impairments.

“Spasticity” is the usual clinical nomenclature to describe the increased perceived resistance during passive elongation of the muscle during physical examination. Although well recognized, this phenomenon is poorly understood. Its etiology is considered to be either hyperreflexia (Lance, 1980) as a response to muscle stretch, or stiffened muscular tissue (Lieber et al., 2004). Common clinical treatment regimens focus on reducing the hyperactivation by chemical denervation of the muscle (e.g., botulinum toxin) to weaken the muscle or rhizotomy of the dorsal roots to attenuate the reflex loop.

In the *EBioMedicine* paper by Raghavan et al. (2016), an alternative approach was presented, i.e. to target the increased stiffness of the muscular tissue, to release its restraining effects on execution of relevant movements of the upper extremity. They postulated the hyaluronan hypothesis, arguing that the main contributing factor to muscle stiffness in the chronic phase after stroke is an adaption of the muscular tissue through the accumulation of hyaluronan. Injections with off-label human recombinant hyaluronidase were used to counteract the effects of hyaluronan and test the hypotheses in a case series trial.

Next to being a safe procedure a large effect was found on the so-called modified Ashworth scale (MAS). This is a typically clinical phenomenological 4 point ordinal scale that is used to score perceived muscle stiffness. Consequently the MAS does not inform on the etiology of

muscle stiffness and was found to be not very reliable (Fleuren et al., 2010). Nevertheless, the independent blinded assessments of passive and active movement combined with the reported effect sizes are still convincing to argue that a significant change in muscle stiffness was induced. Raghavan and colleagues must be complimented for their innovative approach and carefully exploring this new treatment for muscle stiffness, based on sound, but yet to be confirmed reasoning. The potential efficacy of hyaluronidase injections found warrants further study, also in other disorders characterized by muscle stiffness.

Further studies should overcome the weaker points of the study of Raghavan and colleagues as well as expand on our understanding what causes stiffness in the muscle. Besides a controlled randomized methodology, the next step should include more appropriate outcome measures. Based on recent consensus on concepts of tissue stiffness and hyperreflexia (Noort et al. 2016), instrumented assessments are defined to replace the MAS. Such assessments comprise the measurement of the joint moment and joint angle as a function of time during passive elongation of the muscle, to quantify stiffness employing slow stretch. Furthermore surface electromyographic signals are recorded, to quantify reflex activity, employing fast stretch (Bar-On et al., 2014). These measures will also help to identify the best responders to hyaluronidase, since it is presumed to be effective in cases where tissue stiffness is the main nominator of perceived hyper-resistance. Furthermore, next to these structural outcomes, the assumed association between reducing muscle stiffness (evaluated on the passive muscle) and meaningful gains in functional outcomes of the upper paretic limb (involving active contractions) needs further elaboration, e.g. using 3D kinematic evaluation of relevant upper extremity tasks (Andel et al., 2008).

More fundamentally, as argued before related to Botulinum toxin for upper limb spasticity (Gracies et al., 2015), studies are needed to establish how changes in the neuronal component of spasticity (hyperreflexia) interact longitudinally with the progressive biomechanical muscle tissue changes in various disorders characterized by muscle stiffness. Increased levels of muscular contractions will lead to muscle tissue shortening and/or stiffening, while muscle spindles in stiff tissue will be more sensitive and lower the threshold of stretch reflexes, creating a self-promoting system. Raghavan and colleagues suggested several mechanisms that need follow up especially to generate hypotheses on the timing of the treatment.

The conventional treatment to counteract shortened/stiffened muscle tissue is to apply long term stretch by means of progressive plastering or dynamic orthoses. Recently the response to such mechanically applied long-term stretch was found to be effective by altering fascicle

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strain (Theis et al., 2015). This has been found by applying 3D ultrasound imaging of the muscles, a promising technique to further reveal morphological changes along with the external mechanical behavior. The further use of microendoscopy (Cromie et al., 2013) will reveal information at the level of the sarcomere in stiffened muscles and the effect of hyaluronidase.

Overall, the study by Raghavan and colleagues have shown that injections of hyaluronidase are safe to apply and results in reduced muscle stiffness of upper extremity muscles for more than 3 months after application in the chronic stage in patients with cerebral injury. It is based on a new paradigm on the etiology of muscle stiffness, which is promising but will require extensive follow up to prove its accuracy and clinical value.

Disclosure

The author declared no conflicts of interest.

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