Professor Martin Flück advocates a translational approach in Charcot-Marie-Tooth disease (CMT), the most common inherited neurologic disorder

A translational approach to CMT

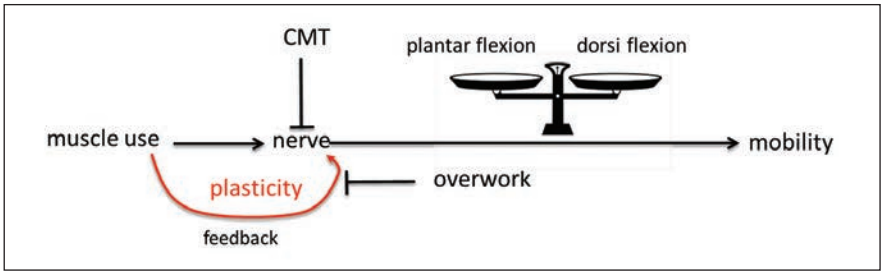
Charcot Marie-Tooth (CMT) disease is the most frequently inherited neurological disorder, arising from motor neuron degeneration and adversely affecting locomotion and balance. It is commonly believed that the deficiencies with CMT are due to an irreversible degradation of motor neuron function due to genetic defects (Braathen *et al.* 2011). However, the stabilisation of musculoskeletal dysfunction by physical therapy and recent observations indicate that this view is not complete. Activity-dependent feedback appears to importantly contribute to the conditioning of musculoskeletal function in CMT patients. Indeed, repeated (strength) exercise is encouraged within each individual patient's capability as it can counteract the muscular deficits in force within a matter of weeks (Lindeman *et al.* 1999).

Intriguingly, the efficiency of physical therapy varies between CMT-patients, and it has recently been argued that inappropriate physical therapy may have detrimental consequences (Vinci *et al.* 2003). In this regard, opposite reactions in antagonistic muscle groups are possible main factors explaining the net effect of CMT on the movement pattern during the gait cycle (Burns and Ouvrier, 2009). Our recent results from animal models fill this gap in knowledge by showing that a myocellular mechanism, which is driven by muscle use conditions, muscle function and maintenance of the motor neuron (Klossner *et al.* 2010). The relevance of this retrograde pathway for the treatment of CMT is currently not appreciated.

To this end we propose the clinical translation of the recently gleaned insight on the molecular process underpinning activity-dependent regulation of motor neuron and muscle function by biomechanical factors. Stimulation of the implicated plasticity would open the door for the sophistication of the treatment of CMT and other neurological diseases (see Fig. 1).

Martin Flück

Fig. 1 Translation of the concept of muscle plasticity into the clinical practice. Essential to this is that activity-dependent feedback conditions foot motor function through the muscle nerve-interaction between plantar and dorsi flexion



Background

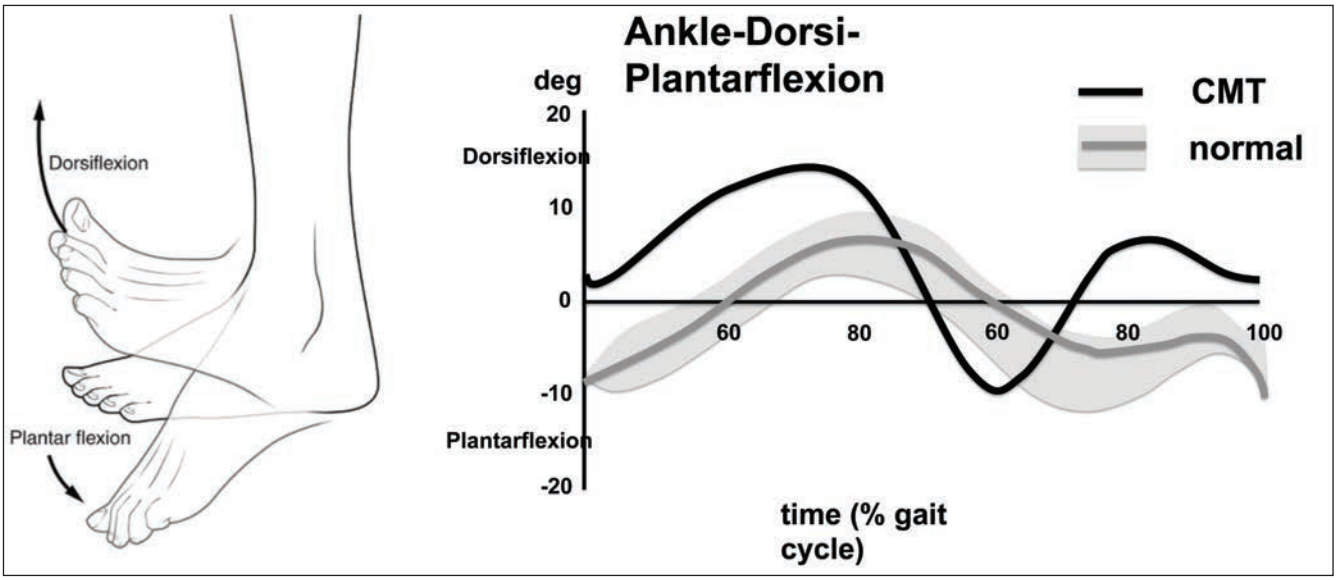
A major neurological disorder: CMT is the most common inherited neurologic disorder (Suter and Snipes 1995). The prevalence of CMT is reportedly high between 10-28 cases per 100,000 in Western societies. CMT patients suffer from a variable degree of motor dysfunction, which adversely affects locomotion and balance. Some patients require the use of forearm crutches, a cane, or ankle-foot orthosis for improved gait stability. Fewer than 5% of patients need wheelchairs.

A slowing of impulse conduction in motor and sensory nerves results in muscle weakness and wasting in the extremities of the body, the feet, the lower legs, the hands, and the forearms. In general, the disease progresses in a centripetal fashion from foot to leg muscle. Lower limbs are therefore more affected than upper extremities. Morbidity in CMT is mainly secondary to distal muscle weakness and foot deformities.

Underlying mechanisms

In most cases, the disease is caused by a myelination defect of motor neurons which renders the downwards propagation of excitatory signals to peripheral muscle inefficient. Pathologies in this category have been classified in CMT type 1 (CMT1). Other deficiencies affecting axon integrity/functionality exist as well and have been termed CMT2. Some 20 genes – for axon proteins and myelin – have been implicated in CMT, and allow the classification into specific (sub)types of the disease (Berciano *et al.* 2012).

The most frequently affected of these is peripheral myelin protein 22 (pmp22). CMT1 subtype A (CMT1A) is the most predominant disease type with 70% of cases being associated with a duplication of the pmp22 gene (Suter and Snipes 1995). The pmp22 gene encodes for a factor that is incorporated into the myelin sheet of neurons and is thought to control myelin thickness (in consequence



saltatory nerve condition). The pathology on the CMT1A disease types is explained by perturbed motor neuron activity due to an aberration in functional pmp22.

Phenomenology of the movement disorder

Biomechanical analysis has revealed that two main defects prevail in CMT patients: a foot drop due to failure in ankle flexion and a defect in plantar flexion (see Fig. 2).

The great variability in these effects is remarkable. These aberrations manifest in different strategies to compensate for deficiencies in the transitions from stance to swing phase of the gait cycle. Therefore CMT patients develop force to a distinctively different extent during the phases of the gait cycle (Fig. 2). This results in pronounced kinematic differences in strike, swing and stance phase, affecting both stability and propulsion of the leg and body mass during walking. Case reports on disease progression indicate that these deteriorations might occur sequentially. Thereby a foot drop, as it is due to defects in dorsiflexors, typically precedes defects in plantar flexion (in ankle flexors). This contention is supported by grouping analysis, which indicates that differences in CMT populations are mainly due to two levels of affection with foot drop with/or without planter flexion (Don *et al.* 2007). Different affections of the relevant leg muscle groups appear involved to a variable degree in these movement deficiencies.

Fig. 2 Illustration showing the two affected antagonistic muscle functions (left) and the consequences of foot movement during a gait cycle (right) in a CMT patient compared to the range of operation in a normal subject

Current and future treatment

Although there is no cure for CMT, there are occupational treatments that can be used to effectively manage its symptoms. The most effective treatment consists of rehabilitation programmes with physical therapy as an active ingredient. Currently, this involves daily heel cord stretching exercises to prevent Achilles tendon shortening. Exercise is encouraged within each individual patient's capability. It has recently been argued that inappropriate physical therapy may have detrimental consequences (Vinci *et al.* 2003).

It is currently proposed that stem-cell and gene transfer therapies are the most promising routes for future cures of CMT. It is our perception that the acknowledged contribution of physical factors for the treatment of CMT is undervalued in current attempts to develop new therapies. This is indicated by impressive increases in maximal voluntary force in CMT patients after strength training. For instance, the force produced during maximal voluntary contraction was increased by 20% within eight weeks of training, being composed of three exercise bouts a week (three sets of 25 contractions to lift a weight corresponding to 60% of the maximal force of a single contraction; Lindeman *et al.* 1999). These results show that use-related factors play an important part in the conditioning of motor performance in this neurological disease. The systematic inclusion of exercise in future rehabilitative strategies to treat and manage Charcot-Marie-Tooth disease patients thus warrants exploration.

Gaps in knowledge

The commonly shared view is that the movement disorder of CMT patients is due to nerve degeneration *per se.* The involvement of different muscle groups to the functional deficits of motor function is not well understood. The review of the literature indicates an important role of environmental factors for the degree of muscle affection in CMT patients. Specifically, a role for physical activity in the modulation of disease progression is implied. Repeated (strength) exercise can counteract the muscular deficits in force within a matter of weeks (Lindeman *et al.* 1999). The underlying salvage mechanism with reference to the

involvement of neuronal and contractile function in muscle tissues is not known in humans. This possibly relates to trophic interaction between the muscle and which is modulated though muscle activity (Betz *et al.* 1980; Booth Baldwin 2011; Carrasco and English, 2003; Flück and Hoppeler 2003).

Our recent investigations in an animal model for CMT demonstrate an important use-related interdependence of motor neuron deficiencies and muscle performance (see Fig. 3, Klossner *et al.* 2011). These experiments hint at the existence of a motor nerve-directed feedback mechanism, which limits the positive influence of physical activity on motor performance in CMT patients. Specifically, this involves the control of motor neuron morphogenesis and the contractile muscle phenotype via muscle-derived production of myelination factor pmp22.

The observations suggest that a retrograde pathway regulates motor neuron conduct velocity and downstream muscle contraction via activity-dependent modulation of motor neuron myelination and innervation by muscle cell derived factors. This use dependent biological pathway possibly contributes to the observed high degree of variability in the affection of ankle extensor and flexor muscles. This may manifest in a failure in ankle flexion that becomes manifest as a foot drop. Muscular reaction/plasticity in these antagonistic muscles may counteract deficits in the antagonistic ankle extensors (i.e. plantar flexors) that lead to the foot drop. The underlying molecular-physiological mechanism and its specific function and structural implication in the conditioning ankle extensor and flexor muscle performance in CMT patients remains to be tested in the clinics.

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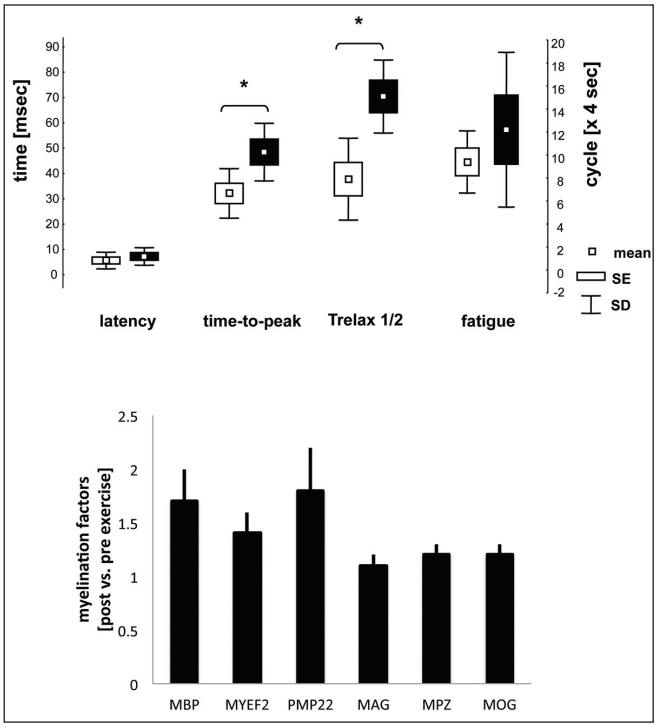

Fig. 3 Summary of the defects in muscle contraction with CMT in a mouse model (top) and alterations in expression of myelinisation factors post exercise in a human muscle (bottom)

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