Journal of Clinical Neuroscience 17 (2010) 874–878

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Correlation between muscle atrophy on MRI and manual strength testing in hereditary neuropathies

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ARTICLE INFO

Article history:
Received 10 August 2009
Accepted 17 November 2009

Keywords:
Charcot-Marie-Tooth
Hereditary motor neuropathy
Neuropathy
MRI

ABSTRACT

MRI shows areas where muscle has been replaced by fat, a process which occurs in neuropathies. The purpose of this study was to investigate the usefulness of MRI in assessing disease severity in Charcot-Marie-Tooth (CMT) and hereditary motor neuropathy (HMN) compared to manual muscle testing (MMT). MRI and MMT correlated well (Spearman's rank correlation coefficient 0.910, 0.789–1.0). MRI was useful to document the extent and pattern of muscle atrophy and fat replacement and to determine the level of denervation. In addition, nerve length dependent denervation was confirmed in both CMT and HMN. MRI will be useful to confirm MMT findings and may be helpful for diagnosis of early or subclinical disease, as well as to further investigate the mechanisms of hereditary neuropathies.

1. Introduction

1.1. Hereditary neuropathies

Inherited peripheral neuropathies are the most common monogenetically inherited diseases of the nervous system with prevalence rates are as high as 1 in 2500.[1] Hereditary neuropathies are therefore a common problem in clinical neurology. Patients typically present with symmetrical weakness and wasting of the small foot and peroneal muscles. This distal atrophy progresses proximally over time and may be associated with foot deformity and sensory loss.

Hereditary neuropathies are subdivided into 3 distinct groups: hereditary motor neuropathies (HMN), hereditary sensory and autonomic neuropathies (HSAN) and hereditary motor and sensory neuropathies (HMSN).[2] HMN are clinically subdivided into categories I to VII,[3] based on mode of inheritance, age of onset, distribution and any unusual features.[4] For example, patients with HMN V may display upper limb weakness or pyramidal signs.[5,6]

Charcot-Marie-Tooth (CMT) disease is also known as hereditary motor and sensory neuropathy (HMSN).[1,7] There are four subgroups of CMT: (i) CMT 1 is demyelinating; (ii) CMT 2 is axonal; (iii) CMT X is X-linked; and (iv) CMT 4 is autosomal recessive. Further subclassifications of CMT depend on molecular genetics and are delineated by letters.[8,9] For example people with CMT 1A have a duplication of the peripheral myelin protein 22 (PMP 22) gene. Because the disease has variable penetrance, CMT may be difficult to recognize in mildly affected people.[10]

1.2. Manual muscle testing: is it accurate?

Manual muscle testing (MMT) is the most commonly used tool for assessing muscle strength. The Medical Research Council (MRC) scale of Great Britain is the accepted grading system.

Recent research on MMT demonstrates that its: (i) accuracy is 78%;[11] (ii) inter-rater reliability is above 82%;[12] (iii) sensitivity is less than 75%;[11] and (iv) specificity is greater than 80%.[11] Aitkens et al. found that the sensitivity and validity of MMT is reduced at higher grades (4−, 4, 4+ and 5).[12] Cuthbert et al. further reported that to be confident that a true change in strength had occurred, MMT scores must change by more than one full grade.[13]

The relatively low accuracy of MMT is most likely due to the test's reliance on the examiner's subjective rating of strength. The gold standard for assessment of muscle denervation in hereditary neuropathies is the measurement of nerve conduction velocities via electrophysiological studies (EPS). EPS can aid diagnosis by determining whether there is sensory involvement and, in the case of CMT, whether the patient has axonal or demyelinating disease. However, EPS requires specialized equipment and expert skill and can be painful for patients. Therefore, on a daily basis, clinicians are more likely to use MMT than EPS when monitoring disease progression.

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doi:10.1016/j.jocn.2009.11.006

1.3. The use of MRI in hereditary neuropathies

No studies have reported the use of MRI for the assessment of muscle atrophy in patients with HMN. Several studies exist for patients with CMT but until recently only descriptive accounts of findings have been available. In 1995 Stilwell et al. found that muscle atrophy and fatty infiltration were more accentuated in the distal regions of affected muscles in 23 patients with CMT.[14] In 1998 Bono et al. ascertained that MRI findings correlated with clinical motor impairment and electrophysiological data in the legs of two patients with CMT 4B (autosomal recessive CMT caused by point-mutations in the myotubularin gene MTMR2).[15] In 2005 Ellegala et al. found that the severity of fatty infiltration tended to increase with the patient's age in seven patients with CMT and one patient with chronic inflammatory demyelinating polyneuropathy.[3]

In 2006 Gallardo et al. reported that muscles which were anatomically more distal, and therefore received the longest branches from the peroneal and tibial nerves, tended to be more severely atrophied in 11 patients with CMT 1A (autosomal dominant CMT with duplication of PMP22 gene).[16] The findings support the hypothesis that the mechanism of motor axon degeneration in CMT 1A is length-dependent.[16] These studies indicate that MRI may be beneficial in assessing disease severity and monitoring disease progression in hereditary neuropathies; indeed, MRI may provide a more objective and clearer picture of denervation than existing methods. To determine whether MRI changes correlate with clinical muscle weakness we conducted MMT in a range of patients with hereditary neuropathies and correlated the results with findings of muscle atrophy as seen on MRI.

2. Materials and methods

2.1. Patients

We used a cross-sectional study design and patients with well-characterized disease were recruited from the CMT database of the Molecular Medicine Laboratory at Concord Hospital in New South Wales. Ethics approval was granted by the Sydney South West Area Health Service Human Research Ethics Committee Concord Repatriation General Hospital (ethics approval number CH62/6/2006-050). Informed consent was obtained for all patients. Patients were excluded if they had a history of multiple surgical corrections to their feet or legs. Eleven patients were initially recruited. Four were later excluded from the study; one because she had undergone multiple corrective surgeries, another because only one lower limb had been imaged and two other patients because their scans were performed elsewhere and the MRI protocol had not been adhered to.

Of the seven included patients, three were male and four were female. Patients were aged 49–82 years with an average age of 68 years. The first two patients had HMN V; they were siblings from a pedigree for which a new HMN locus (7q 34–36) had been found by genetic linkage mapping.[17] Three patients (two siblings from one pedigree and one patient from another) were diagnosed with HMN V; they exhibited distal motor neuropathy with pyramidal signs that showed autosomal dominant inheritance and normal sensory nerve action potentials on EPS. One patient with CMT 1A and one patient with CMT X were found to have *PMP22* and *Cx32* mutations, respectively. All included patients were retained for follow-up. One patient had undergone a metatarsal fusion on the left side.

2.2. Clinical assessment

Two clinicians assessed each patient's strength and MRI findings; each was blinded to the other's results until the study was completed. To gauge the disease duration and rapidity of progression we took a brief history from each patient regarding development of motor milestones, their ability to run or play sport, the presence of foot cramps and whether their shoes were well fitting. A 9-point functional disability scale (FDS) was used to grade each patient's level of function to enable comparison between patients: 0 = normal; 1 = normal with cramps and fatigue; 2 = inability to run; 3 = walking difficulty; 4 = able to walk with a cane; 5 = able to walk with crutches; 6 = able to walk with a walker; 7 = wheelchair bound; 8 = bedridden.[17] The use of the FDS in patients with CMT has been validated in several studies and shown to correlate with clinical and electrophysiological findings and disease duration.[16,18]

Patients' feet were examined for toe clawing, pes cavus and other abnormal posturing. The intrinsic muscles of the foot were assessed for atrophy by observing and palpating the dorsal and plantar aspects of each foot. On the dorsal aspect we examined extensor digitorum brevis, extensor hallicus brevis and the first dorsal interossei; on the plantar aspect we examined abductor hallicus, flexor hallicus brevis and flexor digitorum brevis. The extent of atrophy of the intrinsic foot muscles was graded: 0 = no atrophy; 1 = mild atrophy; 2 = moderate atrophy; 3 = severe atrophy. The range of motion at the ankle joint was also measured with a goniometer. Muscle power was assessed using MMT and graded from 0–5 using the standard MRC scale of Great Britain: 0 = complete paralysis (no movement); 1 = flicker of contraction; 2 = movement across gravity; 3 = movement against gravity; 4− = slight movement against resistance; 4 = moderate movement against resistance; 4+ = submaximal movement against resistance; 5 = normal power.[19]

In the lower leg anterior compartment we assessed tibialis anterior, extensor hallicus longus (EHL) and extensor digitorum longus. In the lateral compartment of the leg we assessed peroneus longus and brevis, in the deep posterior compartment we assessed tibialis posterior (TP), flexor hallicus longus and flexor digitorum longus (FDL). The peroneal muscles could not be isolated from one another during MMT because they work together to evert the foot; their power was therefore assessed together.

MRC grades for each muscle were converted to a 4-point severity score to compare them with the MRI findings. An MRC score of 5 was considered normal and given a severity score of 0. An MRC grade of 4−, 4 or 4+ was designated mild weakness and given a severity score of 1. An MRC grade of 3 was considered equivalent to moderate weakness and given a severity score of 2. MRC grades of 0, 1 or 2 represented muscles that were too weak to contract against gravity, or worse, and were therefore classed as severe weakness and given a severity score of 3.

The muscles of the superficial posterior compartment (gastrocnemius and soleus) were assessed differently. As they are antigravity muscles they were assessed for endurance, rather than strength, by single leg heel raises until the point of fatigue. As gastrocnemius crosses the knee joint, patients performed heel raises to test it using a straight knee. Soleus does not cross the knee joint and was therefore assessed with bent-knee heel raises. The number of single leg heel raises was recorded and used to grade strength: >30 = normal, severity score 0; 21–30 = mild weakness, severity score 1; 10–20 = moderate weakness, severity score 2; <10 = severe, severity score 3. We also assessed each patient's ability to walk on their heels and on their toes.

2.3. MRI protocol

MRI was performed using a 3T Philips Intera Achieva scanner (Philips Medical Systems; North Ryde, NSW, Australia). All patients were studied in the supine position using a torso phased-array coil, centered between both calves at the level of greatest diameter.[15] Imaging was performed in the coronal and axial planes using both