Fatigue in Colchicine Myopathy: A Study of Transcranial Magnetic Stimulation

Kon-Ping Lin[1,4], Yang-Ching Lo[1,4], Chia-Yi Lin[1,3,4], Jen-Tse Chen[1,4,6], Yung-Yang Lin[1,2,4,5], Yi-Chung Lee[1,4], Kwong-Kum Liao[1,4]*

Departments of [1]Neurology and [2]Medical Research, Taipei Veterans General Hospital, [3]Department of Neurology, Chinese Medical University Hospital–Taipei Branch, Departments of [4]Neurology and [5]Physiology, National Yang-Ming University School of Medicine, and [6]Department of Neurology, Cathay General Hospital, Taipei, Taiwan, R.O.C.

Background: Transcranial magnetic stimulation (TMS) is a noninvasive method to assess brain physiology and plasticity. TMS has shown that nervous system excitability may be altered in myopathy, and it presents with motor disinhibition on cortical and subcortical levels. Eight patients who had colchicine myopathy were observed to have fatigue, but they did not have significant weakness. This study investigated whether there was central reorganization to compensate for their muscle strength.

Methods: TMS was applied to study the central compensative mechanism. The TMS parameters included motor evoked potentials, central conduction time, cortical silent period and intracortical inhibition of paired TMS paradigms.

Results: TMS results did not show any significant differences between patient and control groups.

Conclusion: Although central reorganization may occur in patients with hereditary myopathy to compensate for muscular strength, our study did not find any change in cortical excitabilities in acquired myopathy due to colchicine. Muscle fatigue may precede weakness as an early symptom of myopathy. [*J Chin Med Assoc* 2010;73(12):623–627]

Key Words: colchicine, fatigue, myopathy, plasticity, transcranial magnetic stimulation

Introduction

Fatigue is not the same as weakness and it is an independent symptom with an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion. The definition of fatigue is exercise-induced reduction in the maximal capacity to generate force or power output[1] or difficulty in initiation of or sustaining voluntary activities,[2] implying a decrease in performance even in the absence of permanent weakness. Fatigue mechanisms contain a peripheral origin of muscle tissue and a central origin of the nervous system.[3–5] The physiology of exercise-induced fatigue usually contains both components.[4,5]

Fatigue is a common complaint in clinics and is reported in as many as 20% of patients in primary care settings.[2] A high prevalence of fatigue is found in neurological diseases such as stroke,[6] multiple sclerosis,[7] Parkinson's disease,[8] chronic inflammatory demyelinating polyneuropathy,[9] myasthenia gravis,[10] facioscapulohumeral dystrophy, myotonic dystrophy, and hereditary motor/sensory neuropathy type I.[11]

Fatigue is usually underestimated and is generally investigated in the course of or after recovery from a disease. However, it may be an early symptom of patients with neuromuscular disorders and precedes the onset of weakness.

Myopathy is clinically characterized by muscle weakness, particularly low muscle endurance or muscle fatigue. Proximal weakness usually is the hallmark symptom when the diagnosis of myopathy is made. Here, we report 8 patients whose chief complaint was fatigue instead of weakness and they had a final diagnosis of colchicine myopathy. Some unknown mechanisms might compensate for the injured muscles and maintain appropriate muscle strength in these patients.

*Correspondence to: Dr Kwong-Kum Liao, Department of Neurology, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: kkliao@vghtpe.gov.tw • Received: May 25, 2010 • Accepted: July 14, 2010

Table 1. Clinical data of the 8 patients

	Patient							
	1	2	3	4	5	6	7	8
Age (yr)	48	55	62	72	67	42	51	60
Sex	M	M	M	M	M	M	M	M
Fatigue duration (mo)	4	7	2	1	1.5	6	1	2.5
Muscle pain	Yes	No	No	No	No	Yes	Yes	No
Numbness	No	No	No	Yes	Yes	No	No	Yes
DTR	N	N	D	D	D	N	N	N
Creatine kinase* (U/L)								
Before	253	335	766	468	225	664	534	242
After	126	168	106	68	70	38	90	154
FSS								
Before	5.2	5.4	5.4	5.6	5.6	5.4	5.1	5.6
After	2.1	2.3	2.6	2.9	2.6	2.3	2.2	2.7
NCS/neuropathy	–	–	–	Mild	Mild	–	–	Mild
EMG/myopathy	+	+	+	+	+	+	+	+

**The normal range of creatine kinase is 27–168 U/L. M = male; DTR = deep tendon reflex; N = normal; D = decreased; Before = before drug discontinuation; After = after drug discontinuation; FSS = Fatigue Severity Scale; NCS = nerve conduction study; EMG = electromyography.*

It has been hypothesized that, in patients with myopathy, impaired muscular function might be partially compensated by central reorganization.[12] Transcranial magnetic stimulation (TMS) is a well-known method to assess cortical excitability of the motor system.[13] Using TMS, it has been shown that nervous system excitability may be altered in myopathy, and it presents with a motor disinhibition on cortical and subcortical levels.[12] Therefore, we investigated whether there was a change in the motor cortex to compensate for the muscular strength in our patients.

Methods

We included 8 patients (males; age range, 42–72 years) who fulfilled the following criteria: fatigue but without obvious weakness; a history of medication with colchicine; myopathy shown by electrophysiological studies; elevated creatine kinase (CK) levels; and clinical improvement after drug discontinuation (Table 1). History-taking excluded the possibility of hereditary, depression, and endocrine factors. None of the patients had any history of neurological diseases. Fifteen normal subjects (11 males, 4 females) were matched with age and height in the study. The protocol was approved by the institutional review board of Taipei Veterans General Hospital, and all subjects were studied after their signed informed consents were obtained.

The Fatigue Severity Scale (FSS) was applied to evaluate the impact of fatigue on subjects (Table 1). The FSS is a short questionnaire that requires the subject to rate his/her own level of fatigue.[14] To rate the severity of fatigue symptoms, the FSS questionnaire contains 9 statements. FSS was assessed twice in each patient, once at diagnosis and again 6 weeks after drug discontinuation. Subjects were asked to read each statement and circle a number from 1 to 7, depending on how accurately it reflected their condition during the last week and the extent to which they agreed or disagreed that the statement applied to them. A low value (e.g. 1) indicated strong disagreement with the statement, whereas a high value (e.g. 7) indicated strong agreement. The FSS was calculated as the mean score of these 9 items, with answers ranging from 1 (no signs of fatigue) to 7 (most disabling fatigue).[15] Severe fatigue was defined as a mean FSS score of ≥ 5.0.[15]

Using a figure-8 coil, TMS was studied with surface electrodes placed on the right first dorsal interosseus muscle. Two Magstim 200 magnetic stimulators (Magstim Company Ltd., Spring Gardens, Whitland, Carmarthenshire, Wales, UK) connected to a Bistim module were used for studies of intracortical inhibition (ICI) and intracortical facilitation. The data were recorded by a Neuropack M1 machine (Nihon Kohden Corp., Tokyo, Japan).

The coil was positioned over the left motor cortex with the handle pointing to the posterolateral direction,

and the point at which suprathreshold stimuli could produce the highest amplitude motor responses was determined. The point was then marked on a cap to ensure the same stimulating site through the following experiments. Use of visual and auditory feedback from an electromyographic machine helped subjects maintain muscles at relaxation in the assessment of motor threshold (MT), motor-evoked potentials (MEP) and paired TMS studies at constant muscle contraction during study of the cortical silent period.

MT was defined as the intensity to evoke MEP with amplitude $\geq 50\,\mu V$ in at least 5 out of 10 recordings during muscle relaxation. Using 150% MT, we measured the peak-to-peak amplitude and the onset latency of the largest MEP for the further study of motor central conduction time. The cortical silent period was also performed with single pulses at 150% MT during moderate muscle contraction. Ten rectified traces were recorded with a 500-ms sweep speed and 200–500 μV sensitivity. Cortical silent period duration was defined from the turning point of the MEP to the reoccurrence of voluntary electromyographic activity. ICI and intracortical facilitation were studied by using the method proposed by Kujirai et al.[16] During relaxation, 80% MT and 120% MT were applied as the subthreshold conditioning and suprathreshold test stimuli, respectively. Paired stimuli with ISIs of 2, 3, 4, 10, 15 and 20 ms were delivered in a randomized order. At least 5–10 trials were recorded for each condition. The amplitude ratios of conditioning and test MEPs were measured at each ISI.

Nerve conduction studies and electromyography were conducted in each patient. We measured the compound motor action potentials (M) and F responses of the first dorsal interosseus. The formula of motor central conduction time was as follows:

$$\text{motor central conduction time} = \text{MEP} - (\text{F} + \text{M} - 1)/2$$

The largest amplitude of M and F waves was measured from peak to peak. We also calculated the amplitude ratio of MEP/M and F/M in each subject.

The Wilcoxon rank sum test was applied to assess the difference between patient and control groups, and the Wilcoxon signed-rank test was used for comparison before and after fatiguing exercise. Significance was considered at the level of $p \leq 0.05$.

Results

The main clinical findings are summarized in Table 1. The course of fatigue was insidious and progressive (mean, 3.1 ± 2.3 months; range, 1–7 months). The plasma CK value of each patient returned to the normal range 4 weeks after drug discontinuation (before discontinuation, 435.9 ± 206.1 U/L; after discontinuation, 102.5 ± 44.8 U/L; $p = 0.0009$; Table 1). Electrophysiological results were consistent with myopathy in 8 patients and mild axonal neuropathy in 3. These electromyographic findings rapidly resolved 6 weeks after diagnosis and management. Repetitive stimulation at 3 Hz was performed in some patients and this did not show a significant decrement or evidence of neuromuscular junction dysfunction. The C-reactive protein level was not elevated in any patient.

Severe fatigue (FSS ≥ 5) was noted in each patient (patients, 5.41 ± 0.19; controls, 2.12 ± 0.45; $p = 0.0004$; Table 1). Most of the patients described an inability to maintain a sustained effort, which was ameliorated by rest. All of the patients described fatigue as their most disabling symptom, sometimes preventing them from carrying out professional as well as sociofamilial activities. Before discontinuation, FSS was higher in patients than in controls (2.12 ± 0.45; $p = 0.0004$). After discontinuation, they all had a rapid recovery, with a FSS from 5.41 ± 0.19 to 2.46 ± 0.28 ($p = 0.0009$). Electrophysiological results did not show any significant group difference (Table 2).

Discussion

The diagnosis of myopathy in our patients was made 1–7 months after the onset of fatigue. It was difficult for physicians to make an early diagnosis with only a nonspecific complaint of fatigue. Other causes should be considered in our patients in the differential diagnosis of fatigue. Two of our patients (patients 2 and 6) had had fatigue for more than 6 months. Chronic fatigue syndrome was considered for these patients in the differential diagnosis. However, fatigue could be alleviated by rest in these patients but this is not the case for chronic fatigue syndrome.[17] Therefore, these 2 patients did not have chronic fatigue syndrome. Neuropathy was noted in 3 patients whose FSS and CK values decreased after discontinuation but nerve conduction study results did not improve. Therefore, neuropathy could not account for their fatigue. We could not completely exclude the possibilities of anxiety, depression or sleep disturbance, which also might play a role in the symptom of fatigue. However, resolution of the fatigue after colchicine discontinuation strongly supports the diagnosis of drug-induced myopathy. Our report indicates that fatigue may precede weakness and present as the initial manifestation of

Table 2. Electrophysiological data*

	Patients ($n=8$)	Controls ($n=15$)	p
Motor NCS			
M latency (ms)	3.84 ± 0.22	3.74 ± 0.20	0.30
M responses (mV)	19.96 ± 1.44	20.56 ± 1.05	0.44
F latency (ms)	26.23 ± 1.13	27.11 ± 0.86	0.08
F responses (mV)	0.22 ± 0.10	0.26 ± 0.12	0.50
F/M ratio (%)	1.10 ± 0.59	1.24 ± 0.55	0.58
TMS/single stimulation			
Motor threshold (%)	42.8 ± 5.8	40.8 ± 6.1	0.60
MEP latency (ms)	21.69 ± 1.31	22.28 ± 0.98	0.30
MEP amplitude (mV)	2.44 ± 0.81	2.24 ± 0.64	0.70
CCT (ms)	7.11 ± 0.75	7.35 ± 0.55	0.35
MEP/M response (%)	12.18 ± 3.65	10.82 ± 2.79	0.48
Silent period (ms)	141.9 ± 11.1	141.7 ± 11.9	0.99
TMS/paired stimuli			
ISI 2 ms (%)	32.06 ± 5.83	31.68 ± 4.98	0.95
ISI 3 ms (%)	33.34 ± 7.75	34.61 ± 4.31	0.63
ISI 4 ms (%)	42.36 ± 7.86	40.85 ± 7.31	0.61
ISI 10 ms (%)	125.6 ± 10.4	120.7 ± 11.5	0.35
ISI 15 ms (%)	136.5 ± 10.4	132.5 ± 7.3	0.42
ISI 20 ms (%)	144.1 ± 12.9	139.4 ± 8.2	0.37

**Data are presented as mean ± standard deviation. NCS = nerve conduction study; M = motor action potentials; F = F response; TMS = transcranial magnetic stimulation; MEP = motor-evoked potential; CCT = central conduction time; ISI = interstimulus interval.*

drug-induced myopathy. Early recognition may shorten the length and severity of morbidity.

The FSS showed that our patients had significant fatigue before therapy. However, our TMS studies did not show any significant difference between patient and control groups. Our results indicated that fatigue of our patients was due to the muscle itself, i.e. muscle fatigue. This finding is in contrast with the report of Liepert et al,[12] who studied short ICI (SICI) for cortical magnetic stimulation and F response for electrical stimulation in 10 patients with myopathy. They found a reduction of ICI, enhanced F amplitudes, and an increased F/M ratio in myopathic patients, and they concluded that their findings could be explained by a motor disinhibition on cortical and subcortical levels. The difference between the 2 studies could, in part, be due to the different methods and different materials. Colchicine myopathy is an acquired disease. However, patients in Liepert et al's study[12] included 6 facioscapulohumeral muscular dystrophy, 2 limb girdle muscular dystrophy, 1 emerinopathy, and 1 multicore disease. Some of their patients had decreased strength of proximal muscles and limited arm abduction, although the hand function of their patients showed normal strength, similar to our study. The disease duration might have been another variable and seemed to be longer in patients in their study.[12]

Liepert et al[12] showed that SICI was decreased in different muscle diseases, indicating that the effect of myopathy on the brain was independent of its pathology and entity. However, in other series, SICI was not reduced in polymyositits,[18] limb girdle muscular dystrophy,[18] Duchenne muscular dystrophy,[19] or in our patients. There are controversial findings on Duchenne muscular dystrophy. For instance, Di Lazzaro et al[20] found reduced cortical excitability with a higher MT, but this was not found by Yayla et al.[19] Another study using paired stimuli of somatosensory-evoked potentials to assess cortical excitability showed that hyperexcitability was found only in patients with myotonic dystrophy but not in facioscapulohumeral muscular dystrophy.[21] Therefore, the effect of muscle diseases on the brain is still controversial.

In conclusion, our results failed to show a central compensative mechanism for strength in our colchicine myopathy patients. Muscle fatigue may precede weakness as an early symptom of myopathy. Plasma CK levels should be measured to rule out the possibility of muscle injury when a patient presents complaining of fatigue. Early recognition and discontinuation of affected medications may shorten the course of morbidity.

Acknowledgments

The study was supported by research grants from Taipei Veterans General Hospital (V96C1-044) and from the National Science Council of Taiwan (94-2314-B-075-022).

References

1. Vøllestad NK. Measurement of human muscle fatigue. *J Neurosci Methods* 1997;74:219–27.
2. Chaudhuri A, Behan PO. Fatigue in neurological disorders. *Lancet* 2004;363:978–88.
3. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. *Physiol Rev* 2001;81:1725–89.
4. Kent-Braun JA. Central and peripheral contributions to muscle fatigue in humans during sustained maximal effort. *Eur J Appl Physiol Occup Physiol* 1999;80:57–63.
5. Schillings ML, Hoefsloot W, Stegeman DF, Zwarts MJ. Relative contributions of central and peripheral factors to fatigue during a maximal sustained effort. *Eur J Appl Physiol* 2003;90: 562–8.
6. Staub F, Bogousslavsky J. Fatigue after stroke: a major but neglected issue. *Cerebrovasc Dis* 2001;12:75–81.
7. Krupp LB. Fatigue in multiple sclerosis: definition, pathophysiology and treatment. *CNS Drugs* 2003;17:225–34.
8. Havlikova E, Rosenberger J, Nagyova I, Middel B, Dubayova T, Gdovinova Z, van Dijk JP, et al. Impact of fatigue on quality of life in patients with Parkinson's disease. *Eur J Neurol* 2008;15: 475–80.
9. Boukhris S, Magy L, Gallouedec G, Khalil M, Couratier P, Gil J, Vallat JM. Fatigue as the main presenting symptom of chronic inflammatory demyelinating polyradiculoneuropathy: a study of 11 cases. *J Peripher Nerv Syst* 2005;10:329–37.
10. Kittiwatanapaisan W, Gauthier DK, Williams AM, Oh SJ. Fatigue in myasthenia gravis patients. *J Neurosci Nurs* 2003; 35:87–93.
11. Kalkman JS, Schillings ML, van der Werf SP, Padberg GW, Zwarts MJ, van Engelen BG, Bleijenberg G. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. *J Neurol Neurosurg Psychiatry* 2005;76:1406–9.
12. Liepert J, Schoser BGH, Weiller C. Motor excitability in myopathy. *Clin Neurophysiol* 2004;115:85–9.
13. Wong WJ, Chen JT, Kao CD, Shan DE, Lin YY, Hu HH, Wu ZA, et al. Transcranial magnetic stimulation in patients with transient ischemic attacks. *J Chin Med Assoc* 2004;67:229–34.
14. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46: 1121–3.
15. Merkies IS, Schmitz PI, Samijn JP, van der Meché FG, van Doorn PA. Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group. *Neurology* 1999;53:1648–54.
16. Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, et al. Corticocortical inhibition in human motor cortex. *J Physiol* 1993;471:501–19.
17. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994;121: 953–9.
18. Di Lazzaro V, Oliviero A, Tonali PA, Felicetti L, De Marco MB, Saturno E, Pilato F, et al. Changes in motor cortex excitability in facioscapulohumeral muscular dystrophy. *Neuromuscul Disord* 2004;14:39–45.
19. Yayla V, Oge AE, Deymeer F, Gurvit H, Akca-Kalem S, Parman Y, Oflazer P. Cortical excitability in Duchenne muscular dystrophy. *Clin Neurophysiol* 2008;119:459–65.
20. Di Lazzaro V, Restuccia D, Servidei S, Nardone R, Oliviero A, Profice P, Mangiola F, et al. Functional involvement of cerebral cortex in Duchenne muscular dystrophy. *Muscle Nerve* 1998; 21:662–4.
21. Mochizuki H, Hanajima R, Kowa H, Motoyoshi Y, Ashida H, Kamakura K, Motoyoshi K, et al. Somatosensory evoked potential recovery in myotonic dystrophy. *Clin Neurophysiol* 2001; 112:793–9.