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Electrophysiological Findings of Subclinical Lower Motor Neuron Involvement in Degenerative Upper Motor Neuron Diseases

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ABSTRACT

Introduction: The present study is an examination of possible subclinical involvement of lower motor neuron (LMN) in patients with primary lateral sclerosis (PLS) and hereditary spastic paraparesis (HSP) electrophysiologically.

Methods: Nine PLS patients and 5 HSP patients were prospectively analyzed. Jitter measurement with concentric needle electrode (25 mm, 30 G) (CN-jitter) recorded from right extensor digitorum muscle during voluntary contraction with 1 kHz high-pass frequency filter set. European Myelopathy Score (EMS) was used to evaluate disability. The relationship between disability score and jitter values was investigated.

Results: HSP patients had suffered from the disease for longer period of time ($p<0.001$). Mean jitter values of patients with PLS and HSP were 26.5±12.1 μs and 30.8±34.8 μs, and the number of individual high jitters (>43 microseconds) observed in the PLS and HSP groups was 16/180 and 9/100, respectively without a significant intergroup difference. The ratio of patients with an abnormal jitter study were higher in HSP group (60%) compared to PLS (22%) ($p<0.05$). Potential pairs with blocking were present in HSP group (7 of 100 potential pairs) but not seen in PLS patients. EMS values were significantly lower in patients having potential pairs with high jitter and blocking compared to those without high jitter and blocking.

Conclusion: The present study has demonstrated that early signs of LMN dysfunction can be detected electrophysiologically by CN-jitter in patients with UMN involvement. These electrophysiological findings in these patients with longer disease duration and lower clinical scores may be explained by spreading of the disease to LMNs or transsynaptic degeneration and its contribution in disease progression.

Keywords: Transsynaptic degeneration, primary lateral sclerosis, hereditary spastic paraparesis, jitter

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INTRODUCTION

Primary lateral sclerosis (PLS) and hereditary spastic paraparesis (HSP) are diseases of upper motor neuron (UMN) degeneration. Typically, in PLS, the age of onset is the fifth decade, and symptoms often begin in the lower extremities. Bulbar muscle and upper extremity involvement are thought to occur very rarely; however, signs of UMN involvement, in the form of brisk deep tendon reflexes in the upper extremities, were observed (1). Spasticity is more pronounced and predominant than muscle weakness in the affected extremity. In addition to the triad of spasticity, hyperreflexia, and mild weakness; abnormal eye movements, urinary dysfunction, and cognitive involvement may be part of the clinical picture (2). The fundamental defect in PLS is dysfunction of descending corticospinal tracts. It has been reported that neuronal degeneration is confined to the "long descending pathway," and particularly to the corticospinal tract (3). The relative inexcitability of the cortex particularly affects the fastest conducting corticospinal axons that synapse directly on lower motor neurons. Although it has been defined as a progressive disease coursing with pure UMN involvement, many studies have indicated subclinical lower motor neuron (LMN) involvement pathologically and electrophysiologically (2).

HSP, which also demonstrates clinical manifestations of UMN, is a hereditary disease with predominant bilateral spasticity of lower extremities and may be accompanied by bladder dysfunction or sensory complaints. The disease generally spares bulbar region and onsets during adolescence or second and third decades of life (4). Conventional electromyography (EMG) studies will yield only limited information in HSP. However, signs of LMN have been demonstrated in the patients with the presence of spastic paraplegia 4 (SPG4) gene mutation (5). Differential diagnosis between PLS and HSP can be achieved with genetic tests in addition to clinical findings mentioned above (6). Neurodegeneration in HSPs involves primarily sensory and corticospinal tract axons, and arises through a progressive 'dying-back' process starting from the distal ends of the axons (7). The gradual retraction of UMN axons progressively impairs and dysregulates the synapse between UMNs and LMNs.

The aim of this study was to investigate LMN dysfunction, which may be caused by progression of the disease either by spreading to LMNs or transsynaptic degeneration and dying forward mechanism in PLS and HSP, diseases that progress with signs of UMN involvement, but have different pathophysiological mechanisms. To this end, since the earliest sign of

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LMN dysfunction is assumed to be a conduction failure at neuromuscular junction (NMJ), single-fiber EMG that is a sensitive method for assessing the NMJ function could reveal the early signs of LMN degeneration (8, 9). Single-fiber EMG is a method of measuring changes in safety factor at neuromuscular junction in the muscle studied (10). When performed during voluntarily contraction, this technique records the variation in interpotential intervals of 2 individual muscle fibers of the same motor unit between each firing of the motor unit. This variability is called 'jitter' and expressed as mean consecutive difference (MCD) in successive traces. (11, 12). Jitter values in healthy motor unit are within a certain range. In NMJ diseases (e.g., myasthenia gravis or Lambert-Eaton myasthenic syndrome), safety factor at junction is reduced and jitter is increased (13). This calculation is the most sensitive method for diagnosis of NMJ diseases (12). When safety factor is below threshold, block at neuromuscular junction can also be detected using single-fiber EMG. In addition to instances of NMJ disease, high jitter may also be detected in the presence of ongoing denervation and reinnervation in the motor unit as result of conduction failure of newly developed axon sprouts and immature new NMJs (14, 15). Myopathies, channelopaties and diseases with UMN dysfunction showed NMJ dysfunction detected by single fiber EMG (16) Studies, which were conducted on patients with stroke and spinal cord injury reported high jitter values with stimulated single fiber EMG (17).

In this study, the measurement of NMJ function was used to detect LMN involvement by jitter analysis in patients with PLS or HSP without evidence of LMN signs clinically and electrophysiologically in routine EMG studies.

METHODS

The study was performed between January and December of 2015 in the Department of Neurology, Istanbul Faculty of Medicine. From the patients referred to our EMG laboratory, 27 patients with clinical signs of UMN involvement secondary to neurodegenerative disease persisting for at least 3 years were recruited to the study. Thirteen patients, who had already demonstrated LMN involvement findings on needle EMG that fulfilled Awaji and El Escorial criteria, were excluded from the study (18). All patients had botulinum toxin (BTX) injections in lower extremities at least once in their life. However, in none of the patients, upper extremities were used for injections and either of the patients had BTX injections within 6 months prior to electrophysiological examination. As a result, 14 (9 PLS, 5 HSP) patients participated in the study. EMG study was performed using 2-channel EMG device (Dantec Keypoint, Keypoint. net v3.23, Denmark). Approval for the study was obtained from Istanbul University Ethics Committee for Clinical Investigations with protocol #2015/85.

Conduction studies

Sensory and motor conduction of 2 nerves in right upper and lower extremities were tested. Orthodromic median and ulnar, sural and superficial peroneal sensory conduction studies and median motor responses recorded from thenar muscles, ulnar motor responses recorded from hypothenar muscles, tibial and peroneal motor responses recorded from foot muscles were performed as described previously (19).

Needle EMG

Tibialis anterior, gastrocnemius medialis, vastus lateralis, deltoid, biceps brachii, extensor digitorum (ED), and first dorsal interosseous muscles were evaluated bilaterally in all patients using 37 mm 26 G concentric needle electrode with band pass filter setting of 2Hz-10 kHz. Spontaneous pathological EMG activity was measured at sweep speed of 10 ms/div and screen sensitivity of 50 µV/div. MUP configuration during voluntary contraction was evaluated at screen sensitivity of 200 µV/div.

Jitter analysis

For assessing NMJ function, jitter measurement with disposable concentric needle electrode (CN-jitter) was used (20, 21). Concentric needle electrode with small recording surface area (25 mm, 30 G, 0.031 mm^2) was preferred to record single-fiber like action potentials during voluntary contraction of right ED muscle. High-pass filter of the amplifier was set to 1 kHz. (22). Clearly defined action potentials consisting of positive and negative peaks with sharp rise times and stable shapes and without shoulder or notch were recorded with needle position at highest amplitude. Recording was performed when the motor unit under examination attained constant firing rate, and care was taken to avoid changes in the configuration of the potentials during recording (23, 24). The mean consecutive difference (MCD) in the interpotential interval between the negative peaks of the two acquired potential pairs observed in at least 60 consecutive traces (screen sensitivity 0.2 mV/div, screen sweep speed 0.5 ms/div) were accepted as jitter (22, 25). Total of 20 potential pairs were recorded in ED muscle in each patient. Individual MCD and mean MCD values were analyzed for each patient. MCD values were evaluated according to the normal values defined recently for CN (22). The CN-jitter study was considered abnormal if more than 10% of the potential pairs had high jitter values (>43 µs) or if there was high mean MCD according to the reference values (>30 µs) (22).

Evaluation for the presence of disability

European Myelopathy Score (EMS) was used to assess disability (26). Signs and symptoms of the patients were evaluated in categories of gait disorders, urinary dysfunction, handwriting, eating disorders, proprioception/ coordination and paresthesia. Low score indicates more severe forms of disability. Disability scoring as follows: 17–18 points, normal; 13–16 points, stage 1; 9–12 points, stage 2; and 5–8 points, stage 3.

Statistical analysis Non-parametric unpaired test, Mann-Whitney U, was used to compare mean jitter values between PLS and HSP patients and the ratio of abnormal MCD values were compared using chi-square test. Relationship between degree of disability and EMG findings was also analyzed with non-parametric tests.

RESULTS

Patients

Total of 9 PLS (5 male, 4 female) and 5 HSP (3 male, 2 female) patients were enrolled in the study; there was no intergroup gender difference (Table 1). Mean age of the patients in PLS and HSP groups was 50.7 years (range: 38–61 years) and 39.2 years (28–46 years), respectively. PLS patients were relatively older than HSP patients ($p<0.001$). Mean disease duration in PLS and HSP groups was 6.4 years (3–12 years) and 16.6 years (14–20 years) respectively. HSP patients had suffered from the disease for longer period of time ($p<0.001$). Mean disability scores were 10.1 and 9.6 points for PLS and HSP patients respectively ($p>0.05$) (Table 1).

Table 1. Clinical and demographic findings of the patients

	PLS, n=9 Mean ± SD (min-max)	HSP, n=5 Mean ± SD (min-max)	p
Age (years)	50.7±0.6 (38–61)	39.2±0.7 (28–46)	<0.001
Mean disease duration (years)	6.4±3.3 (3–12)	16.6±2.4 (14–20)	<0.001
EMS	10.1±1.7 (7–13)	9.6±3.2 (5–14)	0.07

EMS, European myelopathy score; HSP, hereditary spastic paraparesis; PLS, primary lateral sclerosis.

Table 2. MCD values of the patients

	PLS	HSP	p
The average of MCD	26.5±12.1 (7.7–73.3)	30.8±34.8 (8.1–235)	0.127
The number of potentials with high jitter (>43 µs)	16/180 (8.9%)	9/100 (9%)	0.567
The number of patients showing potentials with high jitter	4/9 (44.4%)	3/5 (60%)	0.349
The number of patients with high mean MCD (>30 µs)	2/9 (22.2%)	3/5 (60%)	<0.001
The average of mean MCD calculated for each patient	24.2±4.9 (20.1–42.4)	30.9±8.5 (22.2–42.4)	<0.001
The number of potential pairs with blocking	0/180	7/100	<0.001
The number of patients with potential pairs with blocking	0/9	3/5	<0.001

MCD, mean consecutive difference; HSP, hereditary spastic paraparesis; PLS, primary lateral sclerosis.

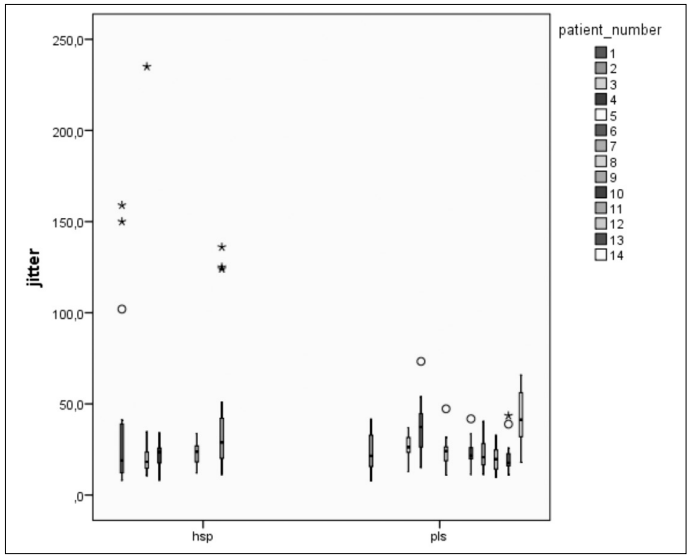

Figure 1. Distribution of individual jitter values according to disease group (PLS, primary lateral sclerosis; HSP, hereditary spastic paraparesis).

Nerve conduction studies

Results of sensory and motor nerve conduction studies of the patients were within normal limits.

Needle EMG

Neither of the muscles studied did not fulfill the criteria for acute and chronic denervation according to Awaji criteria (27).

CN-jitter

In PLS patients, MCD values calculated from 180 potential pairs varied between 7.7 and 73.7 µs, with average value of 26.5±2.1 µs while MCD values calculated from 100 potential pairs recorded in HSP patients ranged between 8.1 and 235 µs, with average value of 30.8±4.8 µs (Table 2). There was no significant difference between total pooled average MCD values of PLS and HSP patients (Mann-Whitney U test, p=0.118). The average of the mean MCD of the 20 potential pairs recorded from each individual patient was 24.2±4.9 µs (20.1–42.4 µs) and 30.9±8.5 µs (22.2–42.3 µs), in 9 PLS patients and 5 HSP patients respectively, revealing a significant difference between groups (Table 2).

Sixteen of 180 (8.9%) MCD values calculated in PLS patients, and 9 (9%) of 100 MCD values calculated in HSP patients were high (>43 µs) (Table 2). Significant difference was not detected in the ratio of the pairs with high jitter between groups. Sixteen pairs with high jitter were detected in 4 of patients with PLS (44%); none was observed in the remaining 5 patients. Nine pairs with high jitter were detected in 3 of patients with HSP (60%), and remaining 2 patients had no high jitter values. The ratio of patients having potential pairs with high jitter tended to be higher in HSP group without reaching significance. Potential pairs with blocking were present in HSP group (7 of 100 potential pairs) but not seen in PLS patients (Table 2, Figure 1). Mean disease duration did not show difference between patients having potential pairs with and without high jitter.

Two patients in PLS group (22.2%) and 3 patients in HSP group (60%) demonstrated high mean MCD values (>30 µs) and more than 10% potentials showing high individual jitter (>43 µs) showing a statistically significant intergroup difference (Table 2).

No difference was detected in EMS scores between PLS and HSP groups (Table 1). Among all patients, mean EMS value was lower in patients (8.7±1.9) with high jitter value compared to those without high jitter (10.1±2.3, p=0.005). The EMS score was lower in patients having potential pairs with blocking in CN-jitter analysis than the patients having potential pairs without blocking (Table 3).

Table 3. The mean EMS (European Myelopathy Scores) values in groups having potential pairs with high jitter and blocking

	EMS	p
Presence of potential pairs with high jitter		
Yes	8.7±1.9	0.005
No	10.1±2.3	
Presence of potential pairs with blocking		
Yes	7.6±3.2	0.006
No	9.9±2.3	

DISCUSSION

The present study has demonstrated that subclinical electrophysiological findings of NMJ dysfunction can be detected in patients with UMN involvement but without obvious ongoing denervation and reinnervation in conventional EMG. CN-jitter analysis was abnormal in 2 of 9 PLS patients, and in 3 of 5 HSP patients, with statistically significant intergroup difference. Significantly higher jitter values observed in HSP group compared with PLS group was notable finding, as well as neuromuscular

conduction block, found in only HSP patients. NMJ dysfunction might resulted from either presynaptic dysfunction of surviving lower motor neurons or newly developed immature NMJ formed via collateral reinnervation as a result of functional loss of lower motor neurons. Although the later should cause acute and chronic denervation in needle EMG examination, subtle changes are not easy to recognize without performing quantitative MUP analysis.

PLS has been defined as a progressive disease coursing with pure UMN involvement. However, studies have indicated presence of subclinical LMN involvement (2). In two different studies performed by Le Forestier et al. (12), signs of reinnervation were demonstrated in biopsy specimens of deltoid and quadriceps muscles in patients with PLS (28). In these studies, electrophysiological studies performed using only conventional EMG did not reveal lower motor neuron dysfunction.

In our study, increased jitter value was detected in both HSP and PLS patients, but was much higher in HSP patients. Presence of neuromuscular block (12) in this group also differentiated HSP patients from those with PLS. This might be due to longer duration of disease in HSP compared with PLS. Another finding was discerned in EMS scores. Statistically significant correlation existed between EMS score using functional criteria and high jitter values. In other words, as the disease progresses, number of abnormal jitters increased similar to disability degree. These findings were similar to the ones reported with stroke patients showing higher jitter in longer disease duration (17).

The reason for high jitter in patients with degenerative syndromes primarily presented with UMN dysfunction can be explained by several mechanisms. First one is the progression of the disease by spreading to LMNs. PLS is a progressive disorder starting from one region and spreading to other regions. In a disease duration of a decade, patients with PLS developed LMN signs which can be either minor or widespread involvement resembling amyotrophic lateral sclerosis (ALS), (29, 30). Similarly, in some forms of HSP, signs of LMN dysfunction present supporting HSP is not a pure UMN disease (31). This kind of progression can be a result of LMN involvement in addition to or secondary to UMN dysfunction. The latter can be defined as the disease progression which may be explained by mechanism of transsynaptic degeneration. A dying-forward hypothesis is proposed as a potential link between UMN and LMN dysfunction, with corticomotoneuronal hyperexcitability mediating LMN degeneration via a transsynaptic glutamatergic mechanism. Decrease in functional motor units following UMN involvement is also described previously as a pathophysiological mechanism (32, 33). Following degeneration of corticospinal fibers in stroke patients, transsynaptic degeneration of motor fibers has been demonstrated. Similarly, in ALS, for which multiple hypotheses have evolved about underlying pathophysiologic mechanism, one of them is that LMN degeneration is a transsynaptic event that develops secondary to corticospinal and corticobulbar neuron loss (1) although the others claimed that involvement of LMN and UMN in ALS are independent processes (34). Our study has demonstrated that LMN can be detected even after long follow-up period in diseases thought to progress with purely UMN involvement. On the other hand, presence of high jitter values in ED muscles of HSP and PLS patients with preserved MUP morphology may indicate a functional loss of lower motor neuron possibly caused by impared control of UMN. This idea can be supported by autopsy studies showing no difference in number and distribution of motor neurons in patients with stroke (35).

High jitter values have been detected in disease models where denervation and reinnervation processes occur in motor units, as well as in NMJ diseases, myopathies, channelopathies and diseases with UMN involvement (16). Indeed, focus of this study was to demonstrate LMN dysfunction developing secondary to upper motor neuron involvement using high jitter values. Supporting this hypothesis, studies showing signs of denervation at early course of disease of UMN dysfunction (36) were pointing a denervation-reinnervation process possibly leading newly developed immature NMJs. However, denervation-reinnervation process should yield neurogenic MUP morphological changes in needle EMG. In our patients who had no obvious changes in MUP morphology high jitter can be explained by a very small-scale denervation-reinnervation cycle. In 1978, Payan J (33) was described the 'Blanket Principle' showing the lower frequency components of MUP cover the higher ones. Once the high frequency filter rose as in jitter analysis, subtle jiggle hiding under 'blanket' , could be recognized more easily (37).

The most important marker supporting interpretation of higher jitter values in favor of denervation-reinnervation was parameter of fiber density. Fiber density increases much earlier than alteration of MUP configuration in a muscle during reinnervation process. Therefore, concurrent presence of high jitter values and increased fiber density indicate presence of ongoing denervation-reinnervation process. Inability to measure fiber density parameter is a limitation of the present study. However, concentric needle electrode cannot be used to measure fiber density as may be calculated with original single-fiber EMG electrode. Previous reports demonstrated patients with stroke showed increased fiber density as well as neurogenic MUP changes in morphology in chronic stage (38).

In our study, jitter parameters did not show significant difference between patient groups except mean MCD values which addressed an increased value in HSP compared to PLS patients. In addition, the ratio of an abnormal jitter study was tended to be higher in HSP (60%) compared to PLS (22%, Table 2). However, in HSP patients there were extremely high jitter values (Figure 1) which might lead to a statistical flaw. On the other hand, HSP patients tended to have potential pairs with abnormal jitter or block consistent with long disease duration. Of further relevance, potential pairs with high jitter were present in patients who also had severe functional scores. All of these findings delineated an increased jitter values indicated long disease duration and disease severity in concordance with disease progression which might be related to LMN dysfunction caused either by dying forward hypothesis or an independent process.

Considering as a limitation in our study, investigation of LMN involvement using CN-jitter may appear to be more conceivable in lower extremity muscles, where clinical involvement is prominent. However, in this study ED muscle was selected for three reasons: Firstly, all of our patients received botulinum toxin (BTX) injections during follow-up period for rehabilitative purposes. As single-fiber EMG examination of BTX-injected lower extremity muscle yields high jitter values, the changes cannot be interpreted in favor of transsynaptic degeneration. Secondly, the patients may have difficulty to contract lower extremity muscles voluntarily and sustain this contraction at stable level predominantly due to UMN involvement. Since there is a motor unit firing instability related to UMN involvement, lower extremity muscles were not preferred for CN-jitter analysis during voluntary contraction. Although stimulated CN-jitter could overcome this difficulty, BTX-injected muscles still complicate the interpretation of data. Finally, reference values for CN-jitter recorded from lower extremity muscles have not yet been described. For above mentioned limitations, we chose ED muscle for jitter analysis in this study. Although lower extremities were affected more severely and initially in HSP, we also manage to show increased jitter values in ED muscle.

Another limitation of our study was the effect of BTX in the muscles away from the injection side described previously (39, 40). Although this effect

loses its strength over time, increased jitter in ED muscles in our patient group can be a result of BTX. However, it is so hard to find BTX naive patients with so long disease duration. On the other hand, some studies suggested that patients showing no symptoms of botulism after BTX injections, had low risk of distant effects of BTX revealed by single fiber EMG (39, 40).

In conclusion, early signs of LMN dysfunction can be detected electrophysiologically by CN-jitter in patients with UMN involvement. High jitter in these patients with longer disease duration and lower clinical scores may be explained by progression of the disease either by spreading to LMNs independently or by transsynaptic degeneration.

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Ethics Committee Approval: Approval for the study was obtained from Istanbul University Ethics Committee for Clinical Investigations with protocol 2015/85.

Informed Consent: Written informed consent was obtained from all participants.

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