

Restless Legs Syndrome in Hemodialysis Patients: Clinical and Electrophysiological Study

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Background: Hemodialysis-related restless legs syndrome (HD-RLS) is a common sensorial and motor disorder. The diagnosis of this disease is based on clinical criteria, and it has recently been proposed to use physiological parameters of the nerves related to the duration of the F wave as a supplementary diagnostic modality. The aim of the study is to determine the value of these parameters in the diagnosis of HD-RLS by comparing the differences between patients with HD-RLS and hemodialysis patients without RLS (HD-nRLS).

Methods: A total of 20 HD-RLS patients, 33 HD-nRLS patients, and 30 age-and gender-matched healthy controls (HCs) were included in the study. The motor nerve conduction of the median and ulnar nerves in the upper limbs, as well as the tibial and peroneal nerves in the bilateral lower limbs, and the sensory nerve conduction of the sural nerve bilaterally and the superficial peroneal nerve, along with the F waves of the ulnar nerves, median nerve, and bilateral tibial nerve, were assessed.

Results: Both groups of HD patients had variable levels of axonal degeneration and demyelination, with the HD-RLS patients having more severe lower limb involvement. The HD-RLS patients showed an extension of the F-wave duration (FWD) of the bilateral tibial, median, and ulnar nerves, along with an increased ratio between FWD and compound muscle action potential duration (CMAPD).

Conclusion: Peripheral neuropathy occurs in patients with HD-RLS, and the FWD/CMAPD ratio could potentially serve as an adjunctive diagnostic tool for HD-RLS.

Keywords: Restless legs syndrome, F wave hemodialysis, peripheral neuropathy

Introduction

Restless legs syndrome (RLS) is defined by an uncontrollable compulsion to move and recurrent limb movements, usually happening at night or during periods of inactivity.¹ The pathophysiological mechanisms responsible for RLS are not fully known and can be categorized into two types: primary RLS and secondary RLS,² which frequently appears in patients who are undergoing hemodialysis.^{3,4} The International Restless Legs Syndrome Study Group (IRLSSG) created diagnostic criteria for RLS that primarily consider patients' symptoms and sensations.⁵ These diagnostic criteria were revised in 2012 to improve the accuracy of the diagnosis.¹ Recently, scholars have proposed that FWD and FWD/CMAPD values could be used as diagnostic indicators for RLS.⁶⁻⁸ FWD is affected by the quantity of motor neurons and central excitability drive, whereas FWD/CMAPD is a crucial measure for evaluating motor neuron function.⁸ Central sensitization is considered one of the pathogenic mechanisms of RLS, which originates from cortical and subcortical dysfunction leading to a decrease in descending spinal inhibition,⁹ thereby causing excessive excitability and dysfunction in the spinal cord.¹⁰ The nerve conduction findings in RLS patients in the aforementioned investigations were within the normal range. However, peripheral neuropathy (PN) is widely observed in patients with end-stage renal disease (ESRD).¹¹ Hence, the purpose of this work was to detect PN in HD-RLS by nerve conduction investigations and to ascertain the significance of FWD and FWD/CMAPD ratio in the RLS diagnosis in HD patients.

Methods

Subjects

The study included 20 HD-RLS patients, 33 HD-nRLS patients, and 30 HCs matched in age and gender without any RLS symptoms. The criteria for inclusion of HD patients were being 18 years of age or older and undergoing a minimum of 90 days of hemodialysis therapy. The exclusion criteria were Parkinson's disease, stroke, multiple sclerosis, spinal cord lesions, rheumatoid arthritis, other autoimmune diseases, and a history of diabetes. HD-RLS patients who match the diagnostic criteria for RLS established by the IRLSSG, medications or chemicals that can trigger or worsen RLS symptoms, as well as patients already undergoing drug treatment, are excluded.¹² The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Affiliated Hospital of Ningbo University Medical College (Decision No. XJS20220907, Date 14/10/2022), and written informed consent was provided by the patients.

Electrophysiological Tests

Electrophysiological evaluations were performed in the EMG laboratory using a Danish Dantec Keypoint 9033a07 six-channel electromyograph (factory no. 40396) that was equipped with surface electrodes. The testing took place from 12:00 to 15:00 at a room temperature ranging from 25 to 28°C. The participants' skin temperature was maintained within the range of 32–34 °C, and the patients remained asymptomatic. Research findings suggest that the conduction velocities of both the median nerve and ulnar nerve are reduced on the side with an arteriovenous fistula.¹³ Consequently, we conducted assessments on the opposite upper limb's left/right median nerve (motor and F-wave), left/right ulnar nerve (motor and F-wave), both tibial nerves (motor and F-wave), as well as both peroneal nerves (motor) and both superficial peroneal nerves (sensory) in the lower limb. The following measures were performed: distal sensory latency (DSL), distal motor latency (DML), conduction velocity (CV), sensory nerve action potential (SNAP) amplitude, and compound muscle action potential (CMAP) amplitude. The F-wave detection involved delivering a stimulus at a frequency of 1 hz for 20 repetitions and measuring the shortest latency, longest latency, average latency, amplitude, and duration (from onset to return to baseline).⁸

Statistical Analysis

Statistical analysis was performed using SPSS v. 26.0 (Chicago, IL). The measurements with normally distributed data were shown as **EQN**, and the count data was expressed as a constitutive ratio. The laboratory results from two groups of HD patients consist of measures of hemoglobin, albumin, serum iron, transferrin saturation, ferritin, folic acid, and vitamin B12. Statistical analysis was performed using the independent sample *t* test for normally distributed data and the Mann–Whitney *U*-test for normally distributed data. One-way analysis of variance (ANOVA) assessed the differences among three groups and performed tests for homogeneity of variance and post hoc comparisons, and gender composition was tested by Pearson's chi-squared test. The bilateral tibial nerve, median nerve, and ulnar nerve FWD/CMAPD ratio were considered the independent variables, while the presence or absence of RLS was considered the outcome variable in order to construct a receiver operating characteristic curve (ROC).

Results

Demographics and Clinical Characteristics

The demographic and clinical features of the participants are shown in [Table 1](#). The three groups did not exhibit any notable disparities in terms of age and gender distribution. The HD-RLS patients exhibited a statistically significant elevation in parathyroid hormone concentration compared to the HD-nRLS patients ($P < 0.019$). Nevertheless, there were no notable disparities observed in hemoglobin, albumin β 2-microglobulin, Kt/V, serum iron, transferrin saturation, ferritin, folic acid, vitamin B12, and vitamin D between the HD patients.

Table 1 Demographic Features of the Study Population

Variable	HD-RLS(n=20)	HD-nRLS (n=33)	HCs (n = 30)	P-value
Age(years)	56.95±11.00	53.72±15.69	50.92±14.84	0.385 ^a
Female/Male	6/14	10/23	9/21	0.491 ^b
HD duration(years)	5.27±4.21	4.66±3.78	NA	0.590 ^c
Hemoglobin(g/L)	117.3±7.6	111.1±13.7	NA	0.072 ^c
Serum albumin(g/L)	41.15±2.45	40.78±3.63	NA	0.703 ^c
β ₂ -microglobulin(mg/L)	34.56±4.35	31.46±7.31	NA	0.080 ^c
Folic acid(ng/L)	14.33±11.94	11.73±10.28	NA	0.408 ^c
Vitamin B12(pg/mL)	824.5±526.0	741.1±456.8	NA	0.549 ^c
Kt/V	1.466±0.219	1.493±0.264	NA	0.702 ^c
Serum iron(umol/L)	15.11±5.37	14.54±6.36	NA	0.247 ^c
Ferritin(ng/mL)	70.06±64.71	87.32±93.27	NA	0.473 ^c
Transferrin saturation(%)	32.01±11.68	29.78±12.92	NA	0.523 ^c
PTH(pmol/L)	430.4±270.8	252.6±178.5	NA	0.006 ^c
Vitamin D(ng)	36.55±12.51	33.97±15.04	NA	0.525 ^c

Note: Data are presented as the mean±standard deviation (range of minemax). HD-RLS=hemodialysis with restless legs syndrome;HD-nRLS=hemodialysis without restless legs syndrome;HCs=healthy controls; NA=not applicable. Kt/V=single chamber urea clearance index PTH=parathyroid hormone a ANOVA. b Fisher's exact test. c Two-sample t-tests.

Nerve Conduction Study

In the investigation of motor nerve conduction, both the tibial nerve and common peroneal nerve in the lower limbs of HD patients from both groups exhibited prolonged DML and decreased CV compared to the HCs, with particularly pronounced differences observed in the HD-RLS patients. Additionally, there was a decrease in CMAP amplitude observed in both groups of HD patients compared to the HCs, although the intergroup comparison did not show statistical significance. Two groups of HD patients exhibited reduced CV in the median nerve compared to the HCs. The HD-RLS patients also demonstrated prolonged distal motor latency and slowed conduction velocity in the ulnar nerve, along with decreased CMAP amplitude in both the median and ulnar nerves, as indicated in Table 2. Both groups of HD patients showed varying degrees of axonal degeneration and demyelination, with greater lower extremity involvement observed in the HD-RLS patients.

Both groups of HD patients exhibited slower bilateral peroneal nerve CV compared to the HCs in terms of sensory nerve conduction. The HD-RLS patients demonstrated a more pronounced decrease and displayed prolonged DSL. Furthermore, within the HD-RLS patients, there was an elongation observed in superficial peroneal nerve DSL and a reduction in CV, specifically on the left side. Both sides of sural nerve and superficial peroneal nerves exhibited decreased SNAP amplitudes in the HD-nRLS patients. (Table 3).

Table 2 Comparison of the Motor Nerve Conduction Parameters in the Study Population

Nerve	Variables	HD-RLS(n=20)	HD-nRLS (n=33)	HCs (n = 30)	P-value
Tibial(left)	DML (ms)	3.97±0.56 ^a	3.57±0.45	3.43±0.68 ^c	0.008
	CMAP amplitude (mV)	9.69±3.14	10.44±2.72 ^b	13.85±3.59 ^c	<0.001
	CV (m/s)	38.77±3.27 ^a	43.09±3.94 ^b	45.70±3.25 ^c	<0.001
Tibial(right)	DML (ms)	4.00±0.82 ^a	3.55±0.62	3.36±0.51 ^c	0.007
	CMAP amplitude (mV)	10.04±2.61	10.44±3.34 ^b	14.12±3.63 ^c	<0.001
	CV (m/s)	38.49±3.13 ^a	42.73±3.16 ^b	44.81±2.58 ^c	0.001
Common peroneal (left)	DML (ms)	4.39±0.95 ^a	3.89±0.47 ^b	3.21±0.50 ^c	<0.001
	CMAP amplitude (mV)	2.89±1.44	2.68±1.17 ^b	4.84±1.62 ^c	<0.001
	CV (m/s)	38.61±2.97 ^a	42.37±2.80 ^b	44.81±3.64 ^c	<0.001

(Continued)

Table 2 (Continued).

Nerve	Variables	HD-RLS(n=20)	HD-nRLS (n=33)	HCS (n = 30)	P-value
Common peroneal (right)	DML (ms)	4.03±0.69	3.83±0.61 ^b	3.24±0.39 ^c	<0.001
	CMAP amplitude (mV)	3.78±1.78	3.36±1.36 ^b	4.60±1.65 ^c	0.024
	CV (m/s)	38.83±3.81 ^a	41.89±3.80 ^b	44.79±2.61 ^c	0.001
Median	DML (ms)	2.02±0.32	1.88±0.25	1.91±0.29	0.222
	CMAP amplitude (mV)	8.52±1.85	8.38±2.66 ^b	9.82±2.03	0.054
	CV (m/s)	42.36±6.83	42.19±8.91 ^b	48.76±3.07 ^c	0.001
Ulnar	DML (ms)	2.88±0.32 ^a	2.52±0.32	2.53±0.37 ^c	0.001
	CMAP amplitude (mV)	7.52±1.62	7.24±1.59 ^b	8.23±1.84	0.100
	CV (m/s)	51.71±4.32 ^a	55.81±5.79	55.06±3.25 ^c	0.011

Note: one-way analysis of variance (ANOVA) a:HD-RLS VS HD-nRLS P<0.05 b:HD-nRLS VS HCS P<0.05 c:HCS VS HD-RLS P<0.05.

Abbreviation: DSL, distal sensory latency;SNAP, sensory nerve action potential;CV, conduction velocity; DML, distal motor latency; CMAP, compound muscle action potential; CV, conduction velocity.

Table 3 Comparison of the Sensory Nerve Conduction Parameters in the Study Population

Nerve	Variables	HD-RLS(n=20)	HD-nRLS (n=33)	HCS (n = 30)	P-value
Sural(left)	DSL (ms)	2.01±0.27	1.85±0.26	1.76±0.29 ^c	0.020
	SNAP amplitude (mV)	19.56±8.47	18.72±10.87 ^b	24.79±10.10	0.079
	CV (m/s)	49.54±5.21 ^a	53.72±4.32 ^b	56.27±5.67 ^c	<0.001
Sural(right)	DSL (ms)	1.90±0.35	1.74±0.29	1.61±0.26 ^c	0.009
	SNAP amplitude (mV)	18.08±8.58	15.93±10.23 ^b	21.31±9.64	0.142
	CV (m/s)	50.01±5.59 ^a	55.18±4.86 ^b	58.30±5.81 ^c	<0.001
Superficial peroneal(left)	DSL(ms)	2.19±0.34	2.05±0.31 ^b	1.87±0.26 ^c	0.003
	SNAP amplitude (mV)	17.10±6.73	16.43±6.95 ^b	21.13±8.43	0.067
	CV (m/s)	44.14±4.59 ^a	48.96±4.61 ^b	53.49±3.91 ^c	<0.001
Superficial peroneal(right)	DSL (ms)	2.19±0.36 ^a	1.98±0.26	1.84±0.21 ^c	<0.001
	SNAP amplitude (mV)	13.43±6.13	16.35±8.82 ^b	21.62±7.87 ^c	0.004
	CV (m/s)	45.96±5.35 ^a	50.27±6.42	51.57±4.72 ^c	0.005

Note: one-way analysis of variance (ANOVA) a:HD-RLS VS HD-nRLS P<0.05 b:HD-nRLS VS HCS P<0.05 c:HCS VS HD-RLS P<0.05.

Abbreviation: DSL, distal sensory latency;SNAP, sensory nerve action potential;CV, conduction velocity.

F-Waves

Bilateral tibial nerve F waves showed prolonged minimum, maximum, and mean latencies in both groups of HD patients. Nevertheless, these alterations were particularly noticeable in patients with HD-RLS. These changes were more pronounced in HD-RLS patients. Notably, the HD-RLS group had a significantly longer FWD than the HCs. No statistically significant difference in FWD was found between HD-nRLS patients and HCs and no differences were observed between the three groups in F-wave amplitude and CMAPD.

The minimum latency, maximum latency, and mean latency of the F wave of the median nerve were longer in the HD-RLS patients than in the HCs. In addition, the minimum latency, maximum latency, and mean latency of the F wave of the ulnar nerve in the HD-RLS patients were also longer than those in the HD-nRLS patients and the HCs. The FWD of both median and ulnar nerves was prolonged in the HD-RLS patients, while no statistically significant difference was found between the HD-nRLS patients and the HCs. No significant differences were found between the three experimental groups in terms of F-wave amplitude and CMAPD. (Table 4).

The HD-RLS patients had significantly higher FWD/CMAPD ratios for the bilateral tibial nerves, median nerves, and ulnar nerves compared to the HD-nRLS patients and the HCs. There was no statistically significant difference in the FWD/CMAPD

Table 4 Comparison of the F-Wave Parameters in the Study Population

F-wave	Variables	HD-RLS(n=20)	HD-nRLS (n=33)	HCs (n = 30)	P-value
Tibial (left)	Minimum latency (ms)	54.28±4.82 ^a	48.35±4.17 ^b	45.94±3.36 ^c	<0.001
	Maximum latency (ms)	58.03±4.74 ^a	51.89±4.54 ^b	48.57±3.28 ^c	<0.001
	Mean latency (ms)	55.97±4.49 ^a	49.86±4.32 ^b	47.22±3.21 ^c	<0.001
	Maximum amplitude (mV)	331.9±152.2	329.7±164.3	342.0±110.6	0.951
	Duration (ms)	28.94±2.55 ^a	15.70±3.01	16.37±2.21 ^c	<0.001
	CMAP duration(ms)	15.74±1.79	15.19±2.15	15.53±2.17	0.626
	FWD/CMAPD	1.85±0.26 ^a	1.05±0.27	1.06±0.10 ^c	<0.001
Tibial (right)	Minimum latency (ms)	54.80±4.50 ^a	48.89±4.52 ^b	46.54±3.21 ^c	<0.001
	Maximum latency (ms)	58.33±5.45 ^a	52.31±4.74 ^b	49.37±3.02 ^c	<0.001
	Mean latency (ms)	56.35±4.59 ^a	50.32±4.54 ^b	47.93±3.03 ^c	<0.001
	Maximum amplitude (mV)	388.8±155.4	329.6±142.1	363.2±124.1	0.361
	Duration (ms)	28.08±2.91 ^a	15.82±2.68	16.25±2.11 ^c	<0.001
	CMAP duration(ms)	15.59±2.05	14.71±2.09	14.81±2.15	0.499
	FWD/CMAPD	1.84±0.26 ^a	1.08±0.26	1.12±0.23 ^c	<0.001
Median	Minimum latency (ms)	27.48±1.44	26.45±2.35 ^b	24.69±1.74 ^c	<0.001
	Maximum latency (ms)	30.42±1.52	29.13±2.73	28.21±2.31 ^c	0.009
	Mean latency (ms)	28.96±1.53 ^a	27.61±2.38 ^b	26.22±1.87 ^c	<0.001
	Maximum amplitude (mV)	234.6±96.9	230.3±101.5	237.4±54.7	0.958
	Duration (ms)	17.15±4.01 ^a	12.11±1.44	11.59±1.46 ^c	<0.001
	CMAP duration(ms)	14.93±1.61 ^a	13.46±1.88	13.30±2.03 ^c	0.009
	FWD/CMAPD	1.16±0.31 ^a	0.91±0.11	0.87±0.07 ^c	<0.001
Ulnar	Minimum latency (ms)	28.09±1.73 ^a	25.80±1.53 ^b	24.56±2.34 ^c	<0.001
	Maximum latency (ms)	30.81±1.96 ^a	28.27±1.80	27.66±2.63 ^c	<0.001
	Mean latency (ms)	29.46±1.82 ^a	26.98±1.47	26.01±2.31 ^c	<0.001
	Maximum amplitude (mV)	308.8±86.5	276.0±87.2	290.1±84.1	0.438
	Duration (ms)	17.32±3.32 ^a	12.78±1.79	12.92±1.94 ^c	<0.001
	CMAP duration(ms)	16.13±1.97	15.01±1.94	14.95±2.47	0.127
	FWD/CMAPD	1.08±0.21 ^a	0.86±0.11	0.87±0.10 ^c	<0.001

Note: CMAP duration=compound muscle action potential duration;FWD/CMAPD =f-wave duration/compound muscle action potential duration. One-way analysis of variance (ANOVA) a:HD-RLS VS HD-nRLS P<0.05 b:HD-nRLS VS HCs P<0.05 c:HCs VS HD-RLS P<0.05.

ratio between the HD-nRLS patients and the HCs. The area under the curve (AUC) for the diagnosis of RLS using FWD/CMAPD of the left tibial nerve was 0.967, with a sensitivity of 95.0% and a specificity of 93.9%. The AUC for the diagnosis of RLS by FWD/CMAPD of the right tibial nerve was 0.973, with a sensitivity of 95.0% and a specificity of 87.8%. When diagnosing RLS using FWD/CMAPD of the median nerve, the AUC value was 0.792, with a sensitivity of 70.0% and specificity of 96.9%. Similarly, The AUC for the diagnosis of RLS using FWD/CMAPD of the ulnar nerve was 0.825, with a sensitivity of 75.0% and specificity of 93.9%. (Table 5)

Table 5 Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value for the Studied Parameters in 20 HD Patients with RLS

Parameters	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Cutoff value	P-value
Tibial FWD/CMAPD(left)	0.967	95.0%	93.9%	90.4%	96.8%	1.41	<0.001
Tibial FWD/CMAPD(right)	0.973	95.0%	87.8%	82.6%	96.6%	1.36	<0.001
Median FWD/CMAPD	0.792	70.0%	96.9%	93.3%	84.2%	1.06	<0.001
Ulnar FWD/CMAPD	0.825	75.0%	93.9%	88.2%	86.1%	1.02	<0.001

Abbreviations: AUC, area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; CMAPD, compound muscle action potential duration; FWD, F-wave duration.

Discussion

The pathogenesis of RLS may be related to spinal cord hyperactivity. Spinal cord hyperexcitability can be caused by changes in sensory neurons, motor neurons, or other neurons.^{14–16} In studies of patients with primary RLS, it has been suggested that FWD/CMAPD ratio could serve as a diagnostic tool for RLS. FWD is generally regulated by two types of neurons: small-diameter slow-conducting neurons and large-diameter fast-conducting motor neurons.¹⁷ In patients with RLS, prolonged FWD is thought to be related to reduced inhibition of small-diameter motoneurons by inhibitory interneurons (Renshaw cells) in the midbrain dopaminergic cell cluster A11.^{17,18} Prolonged FWD suggests increased motor neuron excitability in RLS patients, while a significant increase in the FWD/CMAPD ratio may indicate changes in the regulation of motor neurons in the spinal cord.

The results of our investigation indicate that the FWD/CMAPD ratio of bilateral tibial nerves is a very sensitive and specific diagnostic tool for identifying RLS. The left tibial nerve has a sensitivity of 95.0% and a specificity of 93.9%; the right tibial nerve has a sensitivity of 95.0% and a specificity of 87.8%. In contrast, the FWD/CMAPD ratio of median and ulnar nerves displays higher specificity but slightly lower sensitivity in diagnosing RLS. Congiu et al discovered wonderful disparities within the FWD within the higher and lower limbs and the ratio of FWD/CMAPD among sufferers with RLS patients and the HCs. The tibial nerve FWD and ratio of FWD/CMAPD have proven an excessive level of sensitivity and specificity within the analysis of RLS. On the other hand, the ulnar nerve FWD and ratio of FWD/CMAPD exhibited decreased sensitivity but maintained an excessive level of specificity. Nevertheless, none of the subjects showed altered nerve conduction study data.⁷ Similar research found no variations in motor and sensory nerve conduction between RLS patients and the HCs. Patients with RLS had prolonged FWD of the tibial and ulnar nerves and an increased FWD/CMAPD ratio.^{6–8} Our study found that the F-wave latency of bilateral tibial, median, and ulnar nerves in HD-RLS patients was extended compared to HD-nRLS patients, albeit with low sensitivity and specificity for RLS diagnosis. The FWD/CMAPD ratio possesses greater diagnostic significance and may correlate with motor conduction anomalies in HD-RLS patients.

In our investigation, HD patients had slower motor and sensory nerve CV, as well as decreased CMAP and SNAP amplitudes, which indicated the presence of PN. ESRD patients frequently develop PN with pure axonal sensory-motor neuropathy and mixed sensory-motor neuropathy being the most common kinds,^{11,19} especially when the lower limbs are more affected. A study of PN in HD patients discovered that 100% of the group with clear clinical symptoms had multiple neuropathies, whereas 92.5% of the group without obvious clinical symptoms did. The group with evident clinical symptoms had prolonged motor nerve DML, low CMAP amplitude, and a delayed CV; sensory nerve responses were absent, with decreased amplitude or prolonged latency, and a slowed CV.²⁰ Our study revealed similar findings, with both groups of HD patients exhibiting prolonged DML and decreased CV in the tibial nerve and common peroneal nerve, particularly more pronounced in the HD-RLS patients. Additionally, the CMAP amplitude decreased in both patient groups. In HD-RLS patients, there was a deceleration of the median nerve and ulnar nerve CV in the upper limbs, while CMAP amplitude decreased in HD-nRLS patients. This shows that HD patients have PN in both upper and lower limbs, and the lesions in HD-RLS patients are more severe.

The correlation between RLS and PN or polyneuropathy (PNP) is a subject of contention. A meta-analysis found that the occurrence of RLS in patients with PN/PNP ranged from 5.2% to 53.7%, while the occurrence of PN in patients with RLS ranged from 0% to 87.5%.²¹ Multiple investigations have verified a significantly greater occurrence of PN in patients with RLS.^{22–25} The prevalence of RLS in patients with various PNP etiologies varies significantly across studies. The occurrence rate of RLS in HD patients with PN ranges from 6.6% to 46.6%,^{26–28} which is higher than that of the HCs. The occurrence rate of RLS in patients with diabetic PN/PNP ranges from 10.6% to 40.3%.²¹ Additionally, the occurrence rates of RLS associated with PNP-related diseases include systemic sclerosis at 40.7%²⁹ and rheumatoid arthritis at 25%,³⁰ both higher than those in the control group at 4.9% and 4%, respectively. There is a certain correlation between PN and RLS, but the pathophysiological mechanism remains unclear. Lanza et al suggest that the pathophysiology of RLS may be associated with various mechanisms, such as central inhibitory weakening and peripheral nerve dysfunction.⁹ Building on these findings, Gemignani proposed a model for the mechanism of RLS as a disorder of the flexor reflex circuit,³¹ wherein abnormal peripheral sensory input can trigger spinal excitability upregulation/

sensitization, resulting in premature activation of motor patterns during rest. In our study, HD patients have PN in both upper and lower limbs, which may be related to the increased prevalence of RLS.

The HD-RLS patients had prolonged FWD in the nerves of both upper and lower limbs, in contrast to the HD-nRLS patients and HCs. However, there was no significant statistical distinction between the HD-nRLS patients and HCs. These findings indicate that the excitability of spinal motor neurons was heightened in the spinal cord of individuals with HD-RLS. Previous research has demonstrated that the symptoms of RLS patients are linked to the dysfunction of the dopaminergic system,³² and that iron is a critical cofactor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis.³³ MRI phase image approaches has demonstrated a notable decrease in iron accumulation in the thalamus and dentate nucleus among individuals with idiopathic RLS when compared to the HCs.³⁴ Additionally, HD-RLS patients exhibit diminished iron deposition in the striatum and cerebellum compared to those with HD-nRLS, and this comparatively reduced iron deposition may correlate with an elevated risk of RLS in HD patients.³⁵ The study of cerebral blood flow (CBF) in HD patients showed increased blood flow in the left medial frontal gyrus and bilateral thalamus and decreased blood flow in the left insular cortex compared to normal controls. Compared with HD-nRLS patients, HD-RLS patients showed increased CBF in the right primary motor cortex, suggesting abnormal perfusion of the sensorimotor cortex and basal ganglia associated with altered iron deposition.³⁶ The studies indicate that dysfunction in the subcortical and/or cortical regions leading to reduced descending spinal cord inhibition may be a pathophysiological mechanism of RLS. The significant increase in the FWD/CMAPD ratio supports the notion that the regulation of spinal motor neurons was altered.

Conclusion

HD Patients in both groups experienced peripheral neuropathy, and the HD-RLS group had more profound lesions in the lower extremities. The bilateral tibial nerve ratio of FWD/CMAP provides a superior level of specificity and sensitivity in diagnosing HD-RLS. The ratio of FWD/CMAPD can serve as an adjunct diagnostic tool for HD-RLS.

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Disclosure

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