ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20221514

Neuropathy in multiple sclerosis patients treated with teriflunomide

Ahmet Kasim Kilic[1], Aysegul Akkan Suzan[1*], Anil Bulut[1], Gulhan Sahbaz[1]

SUMMARY

OBJECTIVE: Teriflunomide is an oral medication approved for the treatment of patients with multiple sclerosis. The primary effect of teriflunomide is to reduce de novo pyrimidine synthesis by inhibiting mitochondrial dihydroorotate dehydrogenase, thereby causing cell-cycle arrest. We aimed to investigate the occurrence of peripheral neuropathy, a rare side effect of teriflunomide, in patients receiving teriflunomide.

METHODS: Multiple sclerosis patients receiving teriflunomide (n=42) or other disease modifying therapies (n=18) and healthy controls (n=25) were enrolled in this cross-sectional study between January 2020 and 2021. The mean duration of teriflunomide treatment was 26 months (ranging from 6 to 54 months). All participants underwent neurological examination and nerve conduction studies of tibial, peroneal, sural, superficial peroneal, median, and ulnar nerves by using surface recording bar and bipolar stimulating electrodes.

RESULTS: The mean superficial peroneal nerve distal latency and conduction velocity were significantly slower, and the mean superficial peroneal nerve action potential amplitude was lower in patients using teriflunomide (2.50 ms, p<0.001; 47.35 m/s, p=0.030; and 11.05 μV, p<0.001, respectively). The mean peroneal motor nerve distal latency was significantly longer and amplitude was lower in teriflunomide patients (3.68 ms, p<0.001, and 5.25 mV, p=0.009, respectively). During the study period, treatment switching to another disease-modifying therapy was planned in 10 patients, and all neuropathic complaints were reversed after switching.

CONCLUSION: Teriflunomide has the potential to cause peripheral neuropathy. The awareness of peripheral neuropathy, questioning the symptoms, and if suspected, evaluation with electromyography and switching the therapy in patients under teriflunomide treatment are crucial.

KEYWORDS: Multiple sclerosis. Teriflunomide. Electromyography. Nerve conduction. Peripheral neuropathy. Neuropathic pain.

INTRODUCTION

Teriflunomide is the active metabolite of leflunomide that has been used for treating rheumatoid arthritis and psoriatic arthritis for years[1]. Teriflunomide is the second oral disease-modifying therapy (DMT) that was approved for the treatment of adult patients with relapsing-remitting multiple sclerosis (MS) in 2012[2]. It affects the metabolism of pyrimidines by selectively and reversibly inhibiting dihydroorotate dehydrogenase, which is the rate-limiting mitochondrial enzyme for the de novo pyrimidine synthesis[1]. The restriction in pyrimidine synthesis reduces the proliferation of activated T and B cells, thereby controlling the inflammation in the central nervous system[3]. The effect of teriflunomide on inflammation is not only through pyrimidine metabolism. Li et al. showed that teriflunomide considerably decreases the release of some pro-inflammatory cytokines [i.e., interleukin-6 (IL-6), IL-8, and monocyte chemotactic protein-1] from peripheral blood mononuclear cells and monocytes by a different mechanism other than dihydroorotate dehydrogenase-dependent pathway[4].

The most common adverse events (AEs) reported in patients receiving teriflunomide were diarrhea, nausea, increased alanine aminotransferase, and alopecia (hair thinning). Furthermore, peripheral neuropathy (both polyneuropathy and mononeuropathy) was also reported as a rare AE[2]. A previous study has shown that the incidence of peripheral neuropathy is higher (13 of 1002 patients) in patients under teriflunomide treatment compared to the control group (1.4 and 0.4%, respectively)[2]. If peripheral neuropathy is suspected and confirmed as a consequence of teriflunomide treatment, discontinuation of teriflunomide is recommended[2].

People with MS could have co-occurring neuropathy, either as a consequence of autoimmune mechanism other than the autoimmunity causing MS or secondary to some other factors such as vitamin deficiency, malnutrition, immobilization, drug usage, systemic disease, and so on. Although MS is primarily thought to be a central demyelinating disease, some studies showed peripheral demyelinating neuropathies in MS patients[5-7]. Misawa et al. showed demyelinating features in 3 of 60 patients' nerve conduction studies (NCSs)[7]. The medications used to treat MS can also trigger the occurrence of peripheral neuropathy. Axonal or demyelinating neuropathy with interferon treatment has been reported in several studies[8,9]. Diagnosing

[1]University of Health Sciences, Kartal Dr. Lutfi Kirdar City Hospital, Department of Neurology – Istanbul, Turkey.
*Corresponding author: ayseg_akkan@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on May 17, 2023. Accepted on May 21, 2023.

neuropathies may be difficult or sometimes under-diagnosed as sensory and motor symptoms of MS can mimic or resemble neuropathic complaints. Being aware of patients' signs and recognition are critical as some neuropathies are treatable and preventable. Peripheral neuropathy is a rare AE of teriflunomide. In this study, we aimed to investigate the occurrence of peripheral neuropathy in patients receiving teriflunomide with objective NCSs.

METHODS

This cross-sectional study was conducted between January 2020 and 2021 at a tertiary referral hospital. Patients aged between 18 and 65 years with definite MS diagnosis according to the McDonald criteria 2017, followed at our MS outpatient clinic, as well as healthy appearing controls were recruited for the study. Patients having a high degree of disability [Expanded Disability Status Scale (EDSS) score higher than 5.5 or requiring a walking aid to walk about 100 meters] or weakness and history of a disease that can cause neuropathy (i.e., rheumatoid arthritis, hypothyroidism, diabetes mellitus, systemic sclerosis, alcohol abuse, etc.) were excluded. Informed consent was obtained from all the participants, and the study protocol was approved by the local ethics committee, conforming to the ethical guidelines of the 1975 Declaration of Helsinki (Decision Number: 514/192/6). A total of 42 patients receiving teriflunomide (group 1), 18 patients receiving other DMTs (group 2), and 25 controls were recruited for the study. The mean duration of teriflunomide treatment in group 1 was 26 months (ranging from 6 to 54 months). After the neurological examinations of the patient group, clinical information and demographic data, vitamin B12, fasting blood glucose, glycosylated hemoglobin (hemoglobin A1c, HbA1c) levels were noted, and EDSS scores were calculated. Demographic and clinical data of the controls were also noted. Finally, the participants were referred to the electromyography (EMG) laboratory for electrodiagnostic evaluation.

We performed NCS using an EMG device (Nihon Kohden Corporation Neuropack® X1) with surface recording bar and bipolar stimulating electrodes. All participants underwent routine NCS of tibial and peroneal motor nerves, sural and superficial peroneal sensory nerves in lower extremities, and motor and sensory branches of median and ulnar nerves on non-dominant side in upper extremities. Motor distal latency, conduction velocities (CVs), compound muscle action potential (CMAP) amplitudes and F-wave latencies of motor nerves, and sensory CV and sensory nerve action potential (SNAP) amplitudes of sensory nerves were measured. Sensory NCS were performed antidromically. Normative data for electrophysiological studies were compared to 25 healthy controls. For amplitude and velocity, lower limits (5th percentile) were used and, for latency parameters, upper limits (95th percentile) were used.

For statistical analysis, categorical variables were defined using percentages and continuous variables using mean (standard deviation) (SD) or median and interquartile ranges. Chi-square test was used for categorical variables. Student's t-test or analysis of variance (ANOVA) was used if normally distributed for continuous variables, and Mann-Whitney U or Kruskal-Wallis test was used if not normally distributed. The analyses were performed using IBM SPSS, version 20 (Statistical Package for Social Sciences, Chicago, IL).

RESULTS

DMTs other than teriflunomide were interferon beta-1a, glatiramer acetate, dimethyl fumarate, fingolimod, and ocrelizumab, and two of the patients were followed up without receiving any DMT. The age and EDSS values of the patients varied between 24 and 56 years and 0–5.5, respectively. There was no significant difference between these three groups in terms of gender, age, vitamin B12 level, vitamin D level, fasting blood glucose, and HbA1c value. A detailed analysis is given in Table 1. The disease duration [mean (SD)] was 69.7 (48.2) months in group 1 and 84.2 (44.5) months in group 2, and there was no significant difference between groups (p=0.229). The median EDSS value (minimum-maximum) of patients was 2 (0–5).

In group 1, neuropathic complaints described by patients were as follows: seven patients had numbness, one patient had allodynia, and one patient had burning sensation. With neurological examination, hypoesthesia of gloves-socks type and hyporeflexia were detected in nine patients. No patient from the other two groups complained about having sensory symptoms.

Superficial peroneal SNAP amplitude could not be obtained in one patient in group 1 and one control. The patient had hypoesthesia of gloves-socks type. Carpal tunnel syndrome was found in five patients in group 1, one patient in group 2, and five controls. When patient groups and the controls were compared according to sensory nerves (median, ulnar, sural, and superficial peroneal), there was no statistical difference in the analysis of median, ulnar, and sural sensory nerves. The mean values of the superficial peroneal nerve assessment were significantly different in all three groups. After post-hoc analysis, the mean value of superficial peroneal nerve distal latency was significantly longer in group 1 compared to group 2 and controls, and it was also significantly longer in group 2 compared to controls (2.50, 2.09, and 1.69 ms, respectively, p<0.001).

The mean superficial peroneal SNAP amplitude was lower in group 1 than in group 2 and controls (11.05, 15.61, and 19.45 μV, respectively, p<0.001). The mean superficial peroneal SNAP amplitude was lower in group 2 than controls, but there was no significant difference. The mean superficial peroneal nerve CV value was significantly slower in group 1 than controls (47. 35 and 58.70 m/s, respectively, p=0.030). The mean CV of group 2 was slower than controls, but it was not significant. A detailed analysis is given in Table 2.

When patient groups and the controls were compared according to motor nerves (median, ulnar, tibial, and peroneal), only mean peroneal nerve distal latency and amplitude were significantly different between the three groups. With post-hoc analysis, the mean value of peroneal nerve distal latency was significantly longer in group 1 compared to group 2 and controls (p<0.001). The mean amplitude of the peroneal nerve was significantly lower in group 1 than controls (p=0.009) (Table 3).

Table 1. Demographic and clinical characteristics of the patient and control groups.

	Group 1	Group 2	Control group	p-Value
Number of participants	42	18	25	
Gender (female/male)	35/7	15/3	19/6	
Age	40.57 (9.60)	38.83 (0.69)	40 (0.83)	0.799
Medication (number of patients)	Teriflunomide:42	Interferon beta-1a: 2 Glatiramer acetate: 1 Dimethyl fumarate: 6 Fingolimod:6 Ocrelizumab: 1 None: 2		
Vitamin B12 (pg/mL)	273 (204–394)	264.5 (185.75–351.25)	223 (203–317.25)	0.569
Vitamin D (ng/mL)	20.87 (14.63–34)	27.57 (18.28–29.94)	20 (13.88–23.30)	0.218
Fasting blood glucose (mg/dL)	94.5 (84.25–101)	85.5 (83.25–109.5)	95 (90–101.5)	0.346
HbA1c (%)	5.30 (5.0–5.30)	5.10 (4.7–5.50)	5.15 (4.90–5.45)	0.129

Data are shown as mean (standard deviation) or median (interquartile intervals). pg/mL: picograms per milliliter; ng/mL: nanograms per milliliter; mg/dL: milligrams per deciliter; HbA1c: hemoglobin A1C.

Table 2. Comparison of sensory nerve conduction results in the patient and control groups.

Sensory nerve	Parameter	Group 1	Group 2	Control	p-Value	LL/UL of normal (5th or 95th percentile)
Median	Distal latency (ms) Amplitude (μV) Velocity (m/s)	2.46 (0.31) 31.86 (9.75) 53.38 (5.92)	2.27 (0.26) 37.81 (10.96) 53.89 (6.67)	2.42 (0.23) 34.44 (12.84) 53.88 (5.80)	0.067 0.159 0.928	2.90 16.59 42.09
Ulnar	Distal latency (ms) Amplitude (μV) Velocity (m/s)	1.97 (0.30) 28.22 (14.09) 57.41 (10.78)	1.88 (0.21) 36.21 (10.65) 61.35 (6.04)	2.03 (0.22) 32.38 (12.29) 58.26 (5.75)	0.299 0.083 0.275	2.52 24.66 47.06
Sural	Distal latency (ms) Amplitude (μV) Velocity (m/s)	2.44 (0.29) 16.14 (4.99) 58.01 (6.66)	2.48 (0.48) 19.67 (8.05) 58.42 (9.95)	2.47 (0.41) 18.24 (6.81) 57.42 (8.72)	0.890 0.115 0.919	3.53 8.92 43.64
Superficial peroneal	Distal latency (ms) Amplitude (μV) Velocity (m/s)	2.50 (0.41)*,+ 11.05 (6.11)*,+ 47.35 (19.35)*	2.09 (0.29)* 15.61 (6.49) 54.62 (15.36)	1.69 (0.30) 19.45 (5.57) 58.70 (13.95)	**<0.001** **<0.001** **0.030**	2.24 12.49 48.2

Bold p-values are statistically significant. LL, lower limit (for amplitude and velocity); UL, upper limit (for latency parameters). *Data are expressed as mean (SD). *p<0.05 compared with the control group. +p<0.05 compared with group 2.

Table 3. Comparison of motor nerve conduction results in the patient and control groups.

Motor nerve	Parameter	Group 1	Group 2	Control	p-Value	LL/UL of normal (5th or 95th percentile)
Median	Distal latency (ms) Amplitude (mV) Velocity (m/s) Minimum F-latency (ms)	2.87 (0.41) 13.92 (3.53) 59.18 (5.75) 24.07 (2.04)	2.77 (0.33) 14.83 (3.46) 60.73 (7.85) 23.69 (2.20)	2.96 (0.48) 15.19 (4.00) 59.83 (4.95) 24.12 (2.06)	0.334 0.355 0.659 0.790	3.95 8.6 51.3 27.7
Ulnar	Distal latency (ms) Amplitude (mV) Velocity (m/s)	2.14 (0.48) 14.32 (4.22) 62.68 (13.00)	2.14 (0.33) 14.77 (3.71) 67.40 (6.96)	2.19 (0.34) 13.31 (2.55) 63.26 (8.01)	0.881 0.396 0.280	2.87 9.2 48.3
Tibial	Distal latency (ms) Amplitude (mV) Velocity (m/s) Minimum F-latency (ms)	4.14 (0.80) 11.04 (3.86) 48.51 (5.07) 45.10 (3.79)	3.88 (0.93) 12.65 (4.75) 50.97 (6.96) 44.60 (4.48)	3.83 (0.60) 12.55 (4.01) 49.32 (5.37) 42.91 (2.94)	0.226 0.226 0.300 0.077	4.78 5.18 41.7 50.7
Peroneal	Distal latency (ms) Amplitude (mV) Velocity (m/s)	3.68 (0.59)*,+ 5.25 (1.69)* 53.20 (5.00)	2.95 (0.57) 6.02 (2.08) 54.71 (5.58)	2.95 (0.58) 6.72 (1.90) 55.68 (5.12)	**<0.001** **0.009** 0.156	4.33 3.81 51.6

Bold p-values are statistically significant. LL, lower limit (for amplitude and velocity); UL, upper limit (for latency parameters). *Data are expressed as mean (SD). *p<0.05 compared with the control group. +p<0.05 compared with group 2.

Superficial peroneal SNAP amplitude in 15 patients, superficial peroneal sensory CV in 25 patients, and peroneal CMAP amplitude in 11 patients were lower in group 1 (n=42) when compared with controls (normative data). Furthermore, peroneal nerve distal latency in 37 patients and superficial peroneal nerve distal latency in 11 patients were longer in group 1 according to the normative data. When we classified the patients according to the history of myelitis (n=24) or not (n=67), regardless of groups, only mean peroneal nerve distal latency was significantly higher in patients with myelitis than in patients without myelitis (p=0.039).

During the study period, treatment switching was planned in 10 patients (one patient for breakthrough disease activity and nine patients for the development of neuropathic complaints). Teriflunomide was switched to fingolimod (n=1), dimethyl fumarate (n=6), or ocrelizumab (n=1). The treatment could not be switched in two patients who did not come to regular follow-up.

DISCUSSION

In this study, both axonal and demyelinating features were found in sensory and motor NCS of patients receiving teriflunomide. The mean superficial peroneal nerve distal latency was longer and CV was slower, and the mean superficial peroneal nerve SNAP amplitude was lower in patients receiving teriflunomide in sensory NCS. The mean peroneal nerve distal latency was longer, and CMAP amplitude was lower in patients receiving teriflunomide in motor NCS.

The diagnosis of polyneuropathies in people with MS is challenging due to the accompanying neurological complaints related to brain and spinal cord lesions. It is important to distinguish whether neuropathic complaints are due to MS pathology or as a result of a concomitant polyneuropathy. In this instance, electrodiagnostic studies can be beneficial. With the help of NCS, neuronal damage can be demonstrated objectively in patients with suspicious neuropathy. Peripheral neuropathy in MS could be divided into two categories as MS with chronic inflammatory demyelinating polyradiculoneuropathy (MS-CIDP, 21%) and MS with other non-inflammatory polyneuropathies (mainly axonal, 79%)[10]. MS CIDP may be the coexistence of two different diseases; however, there are different opinions on this issue. MS-CIDP can be due to a similar immunopathogenesis, common antigen between central and peripheral nervous system, or a consequence of immunomodulatory treatment. The common antigens between central and peripheral nervous systems could be myelin basic protein, myelin-associated glycoprotein, or neurofascin[11-13]. Both axonal and demyelinating polyneuropathies have been indicated after interferon beta treatment in MS patients[8,9]. In a study conducted with relapse remitting MS patients, Gorgulu et al. found demyelinating type changes in motor NCS[14]. We found both axonal and demyelinating findings in sensory and motor NCS in MS patients treated with teriflunomide. The findings indicating demyelination were as follows: the mean value of superficial peroneal nerve distal latency was significantly longer; the mean superficial peroneal nerve CV was significantly slower; and peroneal nerve distal latency was significantly longer

in group 1. None of the patients with demyelinating NCS findings met the European Academy of Neurology/Peripheral Nerve Society criteria for CIDP. The mean superficial peroneal sensory SNAP amplitude and the mean peroneal CMAP amplitude were significantly lower in group 1, and these results suggest axonal loss. We could not obtain superficial peroneal SNAP amplitude in one patient in group 1 (indicating axonal loss), and with the suspicion of neuropathy clinically, teriflunomide therapy was discontinued and switched to another DMT. In this study, we observed abnormalities in NCS of peroneal motor nerve and superficial peroneal sensory nerve; however, we did not find any significant abnormality with the sural nerve. The sural nerve forms from the terminal branches of the tibial nerve and common peroneal nerve. Sumner showed that larger-diameter myelinated fibers are more durable against neurotoxicity than smaller-diameter fibers. Furthermore, the areas of compression sites increase the risk of neuronal damage as a consequence of impaired blood nerve barrier[15]. Among them, fibular head is the most common area for common peroneal nerve entrapment at the lower limbs[16].

In our study, peroneal nerve distal latency was significantly longer in patients with myelitis, but this could be affected by the presence of central (spinal) lesions. Axons from the motor neurons in the ventral gray matter of the spinal cord constitute the motor roots and fibers in the peripheral nerves. Therefore, any lesion of the primary motor neuron can result in degeneration of motor fibers throughout the peripheral nerve. By this way, a spinal cord lesion can result in abnormalities on motor NCSs. Additionally, F-wave responses could be longer in MS patients[17]. In our study, we evaluated F-wave responses of tibial and median motor nerves, but we could not find any significant difference.

Our study had some limitations, of which small sample size is the most important one. Another limitation is that patients with spinal lesions were not excluded. We did not evaluate the presence of plexopathy or radiculopathy that might affect NCS. The strength of our study is that, to the best of our knowledge, this is the first study in the literature investigating the development of peripheral neuropathy in MS patients receiving teriflunomide with objective NCS findings in daily practice. Further comprehensive studies with larger sample size are needed to investigate the development of neuropathy in patients using teriflunomide.

CONCLUSIONS

Teriflunomide is a widely used agent known to have the potential to cause peripheral neuropathy in the treatment of MS. Our findings support the neuropathy AE of teriflunomide as stated in previous studies. The awareness of possible peripheral neuropathy AEs in patients treated with teriflunomide and, in the follow-up, questioning the symptoms or signs indicative of peripheral neuropathy are important for treatment planning. If neuropathy is suspected, evaluation with EMG and switching the therapy should be considered.

ETHICAL STATEMENT

The author declares that the research has been conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," and the study protocol was approved by the local ethics committee (Decision Number: 514/192/6).

INFORMED CONSENT

Informed consent was obtained from all participants.

AUTHORS' CONTRIBUTIONS

AKK: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – review & editing. **AAS:** Data curation, Resources, Software, Validation, Writing – original draft, Writing – review & editing. **AB:** Data curation, Validation, Visualization. **GS:** Data curation, Investigation, Resources, Software.

REFERENCES

1. Fragoso YD, Brooks JB. Leflunomide and teriflunomide: altering the metabolism of pyrimidines for the treatment of autoimmune diseases. Expert Rev Clin Pharmacol. 2015;8(3):315-20. https://doi.org/10.1586/17512433.2015.1019343
2. European Medicines Agency. Aubagio EU summary of product characteristics. 2014. Available from: [cited on May, 20, 2015] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002514/WC500148682.pdf
3. Bar-Or A, Pachner A, Menguy-Vacheron F, Kaplan J, Wiendl H. Teriflunomide and its mechanism of action in multiple sclerosis. Drugs. 2014;74(6):659-74. https://doi.org/10.1007/s40265-014-0212-x
4. Li L, Liu J, Delohery T, Zhang D, Arendt C, Jones C. The effects of teriflunomide on lymphocyte subpopulations in human peripheral blood mononuclear cells in vitro. J Neuroimmunol. 2013;265(1-2):82-90. https://doi.org/10.1016/j.jneuroim.2013.10.003
5. Emad MR, Zeinali L, Nikseresht A, Naseri M, Karimian H. Peripheral neuropathy in multiple sclerosis: an electrophysiologic study in

Iranian patients. Acta Med Iran. 2017;55(8):496-501. PMID: 29034645

6. Hahn AF, Hartung H, Dyck PJ. Chronic inflammatory demyelinating polyradiculopathy. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. Philadelphia: Elsevier Saunders; 2005. p. 2221-55.
7. Misawa S, Kuwabara S, Mori M, Hayakawa S, Sawai S, Hattori T. Peripheral nerve demyelination in multiple sclerosis. Clin Neurophysiol. 2008;119(8):1829-33. https://doi.org/10.1016/j.clinph.2008.04.010
8. Abdelhady S, Rashed H. Axonal neuropathy in multiple sclerosis patients treated with interferon β. J Mult Scler (Foster City). 2019;6:224.
9. Kieseier BC, Hartung HP. Polyneuropathy associated with interferon beta treatment in patients with multiple sclerosis. Neurology. 2006;66(6):955; author reply 955. https://doi.org/10.1212/01.wnl.0000218668.17791.cf
10. Suanprasert N, Taylor BV, Klein CJ, Roforth MM, Karam C, Keegan BM, et al. Polyneuropathies and chronic inflammatory demyelinating polyradiculoneuropathy in multiple sclerosis. Mult Scler Relat Disord. 2019;30:284-90. https://doi.org/10.1016/j.msard.2019.02.026
11. Kawamura N, Yamasaki R, Yonekawa T, Matsushita T, Kusunoki S, Nagayama S, et al. Anti-neurofascin antibody in patients with combined central and peripheral demyelination. Neurology. 2013;81(8):714-22. https://doi.org/10.1212/WNL.0b013e3182a1aa9c
12. Ekstein D, Linetsky E, Abramsky O, Karussis D. Polyneuropathy associated with interferon beta treatment in patients with multiple sclerosis. Neurology. 2005;65(3):456-8. https://doi.org/10.1212/01.wnl.0000171858.82527.4c
13. Reich DS, Lucchinetti CF, Calabresi PA. Multiple sclerosis. N Engl J Med. 2018;378(2):169-80. https://doi.org/10.1056/NEJMra1401483
14. Görgülü Ü, Ergün U, Ertuğrul L. Peripheral nerve conductions in relapsing remitting multiple sclerosis (RRMS) patients. J Clin Neurosci. 2020;74:93-7.https://doi.org/10.1016/j.jocn.2020.01.058
15. Sumner AJ. The physiological basis for symptoms in Guillain-Barré syndrome. Ann Neurol. 1981;9 Suppl:28-30. https://doi.org/10.1002/ana.410090706
16. Masakado Y, Kawakami M, Suzuki K, Abe L, Ota T, Kimura A. Clinical neurophysiology in the diagnosis of peroneal nerve palsy. Keio J Med. 2008;57(2):84-9. https://doi.org/10.2302/kjm.57.84
17. Grana EA, Kraft GH. Electrodiagnostic abnormalities in patients with multiple sclerosis. Arch Phys Med Rehabil. 1994;75(7):778-82. PMID: 8024424