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Electrodiagnosis of polyneuropathy, organmegaly, endocrinopathy, M-protein, skin changes syndrome patients with peripheral neuropathy and potential-related risk factors

Guanru Niu[1,*], Yuchen Liu[2,*], Zhen Zhang[1], Siyuan Song[3], Tian Li[4], Yijun Shen[5] and Jihong Dong[1]

[1]Department of Neurology, Zhongshan Hospital Fudan University, Shanghai, China
[2]Department of Endocrinology, Zhongshan Hospital Fudan University, Shanghai, China
[3]Department of Neuroscience, Baylor College of Medicine, Houston, TX, USA
[4]School of Basic Medicine, Fourth Military Medical University, Xi'an, China
[5]Department of Neurology, Shanghai Geriatric Medical Center, Shanghai, China

Abstract

Objectives: To explore the correlation between classification and electrophysiology of polyneuropathy, organmegaly, endocrinopathy, M-protein, skin changes syndrome (POEMS)-related peripheral neuropathy (PN).

[*]equally contribution

Corresponding authors:
Tian Li, School of Basic Medicine, Fourth Military Medical University, Xi'an 710032, China.
Email: fmmult@foxmail.com

Yijun Shen, Department of Neurology, Shanghai Geriatric Medical Center, 2560 Chunshen Road, Shanghai 201104, China.
Email: shenyijun66@163.com

Jihong Dong, Department of Neurology, Zhongshan Hospital Fudan University, 180 Fenglin Road, Shanghai 200032, China.
Email: dong.jihong@zs-hospital.sh.cn

Methods: We analyzed the data of 30 POEMS patients admitted to Zhongshan Hospital affiliated with Fudan University between February 2017 and February 2023. The degree of PN was determined according to its classification. All three groups of patients underwent neuroelectromyography, and the nerve conduction velocity and amplitude of the three groups were analyzed.
Results: The compound motor active potentials (CMAP) of the peroneal, tibial, and ulnar nerves decreased significantly with increasing disease grade, and the motor conduction velocity of the peroneal, median, and tibial nerves decreased significantly in grade 3 compared with grade 1 and 2. The action potential of sensory nerves (sensory nerve action potential) and the conduction speed of sensory impulses (sensory conduction velocity (SCV) in the sural nerve in grade 3 were significantly lower than those in grades 1 and 2. Linear regression analysis showed that there was a linear correlation between CMAP of peroneal nerve and vascular endothelial growth factor. The SCV of the ulnar nerve significantly correlated with the course of the disease.
Discussion: Neuroelectromyography can effectively evaluate the degree of PN in patients with POEMS, providing a reliable reference for further clinical treatment.

Keywords
POEMS, peripheral neuropathy, electrodiagnosis, VEGF, NCS

Introduction

Polyneuropathy, organmegaly, endocrinopathy, M-protein, skin changes syndrome (POEMS)-syndrome, alternatively referred to as Crow-Fukase or Takatsuki syndrome, is an uncommon disorder triggered by an underlying malignancy characterized by a specific set of clinical features.[1] This syndrome is primarily diagnosed based on the presence of polyradiculoneuropathy, clonal plasma cell disorder, sclerotic bone lesions, and elevated levels of vascular endothelial growth factor.[2,3] Secondary or minor characteristics encompass organomegaly, endocrinopathy, extravascular volume overload, papilledema, thrombocytosis, and distinctive skin alterations. Owing to its rarity, POEMS syndrome is frequently misdiagnosed as other neurological conditions, with chronic inflammatory demyelinating polyradiculoneuropathy being a common misdiagnosis.[4] The diagnosis of POEMS syndrome heavily relies on the presence of peripheral neuropathy (PN), and electromyography (EMG) proves to be a valuable tool in this regard. However, the potential use of EMG data to evaluate the extent of PN in individuals with POEMS syndrome has not been thoroughly investigated.

Neuroelectromyography can objectively reflect changes in peripheral nerves and is often used to diagnose diabetic PN. Some studies have shown that EMG can be used to distinguish POEMS from other PN-related diseases, such as chronic inflammatory demyelinating polyneuropathy (CIDP) and Monoclonal Gammopathy of Uncertain Significance-related neuropathy.[5,6] The pathophysiology of nerve damage in POEMS syndrome remains unclear, but platelet aggregation, degranulation, ischemia, and small vessel platelet thrombosis may contribute to a loose endothelial barrier, leading to the leakage of proinflammatory cytokines like interleukin-12, increased vascular endothelial growth factor (VEGF) production.[7–9] The nerve conduction detection of points patients usually manifests as: the motor and sensory nerve conduction velocities of the upper and lower limbs can be observed with prolonged latency or slowed nerve conduction velocity (NCV) at the motor terminals of one or more nerves, or accompanied by a decrease in

wave amplitude. POEMS PN usually starts in both lower limbs and gradually progresses upwards. Usually accompanied by numbness, tingling, and chills, followed by symptoms of weakness. As the disease progresses, motor symptoms become more prominent than sensory symptoms.[10–12] These unique features serve as valuable markers for differentiation between POEMS syndrome and conditions like CIDP and neuropathy associated with anti-myelin-associated glycoprotein antibodies, mitigating the risk of duplicative findings. Electrophysiologic studies play a crucial role as a diagnostic tool when assessing individuals with suspected demyelinating neuropathies.[13] Many investigations have delved into the application of nerve conduction studies (NCSs) and EMG to distinguish POEMS from other forms of PN. However, limited research has been conducted to investigate the relationship between the EMG results and the severity of PN specific to POEMS syndrome.[5] This study focused on a cohort of 30 patients diagnosed with POEMS who were admitted to Zhongshan Hospital, affiliated with Fudan University, between February 2019 and February 2023. This study aimed to evaluate the diagnostic utility of neuroelectromyography, specifically in relation to the extent of PN, in individuals with POEMS. Our findings indicate that EMG not only plays a crucial role in diagnosing PN but also provides valuable insights into the severity of neuropathic conditions.

Methods

Subjects

This observational retrospective study took place at Zhongshan Hospital, Fudan University. Thirty patients diagnosed with POEMS syndrome between February 2017 and February 2023 were included in this study. All patients fulfilled the following criteria for the diagnosis of POEMS syndrome: (1) mandatory major criteria including polyneuropathy and monoclonal plasma cell disorder; (2) other major criteria including the presence of elevated VEGF, sclerotic bone lesions, or Castleman syndrome; and (3) minor criteria including organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema, and thrombocytosis. These criteria were used to establish the diagnosis of POEMS syndrome in our patient cohort[4] . We collected 46 patients who completed EMG due to the appearance of peripheral nerve symptoms, but according to the exclusion criteria of individuals with other possible underlying response of PN, including diabetes mellitus, advanced renal disease, alcohol, vitamin B12 deficiency, and adverse reactions to medicine were excluded. Furthermore, participants with a disease duration of ≥ 5 years were excluded to reduce potential confounding effects arising from current conditions during the analysis. A total of 16 individuals were excluded from this section, so we included 30 eligible patients for statistical analysis (Figure 1).

PN grading refers to the Toronto Clinical Scoring System for disease grading diagnosis and is mainly based on three aspects: neurological symptoms, neural reflex, and sensory function examination.[14] If there were no symptoms, one point was scored. Among them, neurological symptoms such as lower limb numbness, pain, needle-like sensation, fatigue, unstable gait, and similar symptoms in the upper limbs will be scored 1 point for each symptom. Neuroreflexes are scored on both sides, with 1 score for symptoms weakened, 2 scores for disappearance, and 1 score for sensory dysfunction.

PN was classified as mild or grade 1 (6–8 points), moderate or grade 2 (9–11 points), and severe or grade 3 (12–14 points).

Demographic and clinical characteristics (age, sex, and duration), laboratory examinations (serum VEGF levels), and electrophysiological diagnostic information of the patients were extracted using a retrospective chart review. In this study, VEGF levels were assessed pre-treatment through an enzyme-linked immunosorbent assay.

Electromyography

Nerve conduction tests were conducted using a Medoc electrogram from Medoc Company in Israel, as reported in our previous research.[15] The subject was in a clear state and fully relaxed, and the surrounding environment was clean and quiet without interference. Throughout the tests, the indoor temperature was maintained at 22–24°C, and the skin temperature was maintained at 32°C or above. Surface electrodes were used to stimulate the proximal portion of the nerve through the skin. Motor-evoked action potentials were obtained at the distal end, and NCV was measured.

Observation indicators

The main detection indicators were (1) Motor nerve conduction: The compound motor active potentials (CMAPs) and the motor conduction velocity (MCV) of the median and ulnar nerves in both upper limbs and the tibial and common peroneal nerves in both lower limbs. (2) Sensory nerve conduction: The median and ulnar nerves were selected in the upper limbs, the sural nerves were chosen in the lower limbs, and sensory nerve action potential (SNAP) and sensory conduction velocity (SCV) measured. The diagnosis of the patients was based on the normal values of various age groups in the EMG room of our hospital as a reference.

Statistical analysis

The descriptive summary was presented as the median and standard deviation for continuous variables. The Kruskal–Wallis, Chi square test, or Fisher's exact test (as appropriate) was used for comparisons between the three groups. VEGF and other risk factors were selected for logistic regression analysis to explore independent determinants for predicting nerve injury.

Result

Demographic and electrophysiological characteristics

The study included a total of 30 individuals diagnosed with POEMS syndrome, comprising 17 female and 13 male patients, and the main demographic and electrophysiological features of patients in the study are summarized in Table 1. Among all the subjects, five had Castleman's disease and seven had multiple myeloma. The mean age, disease

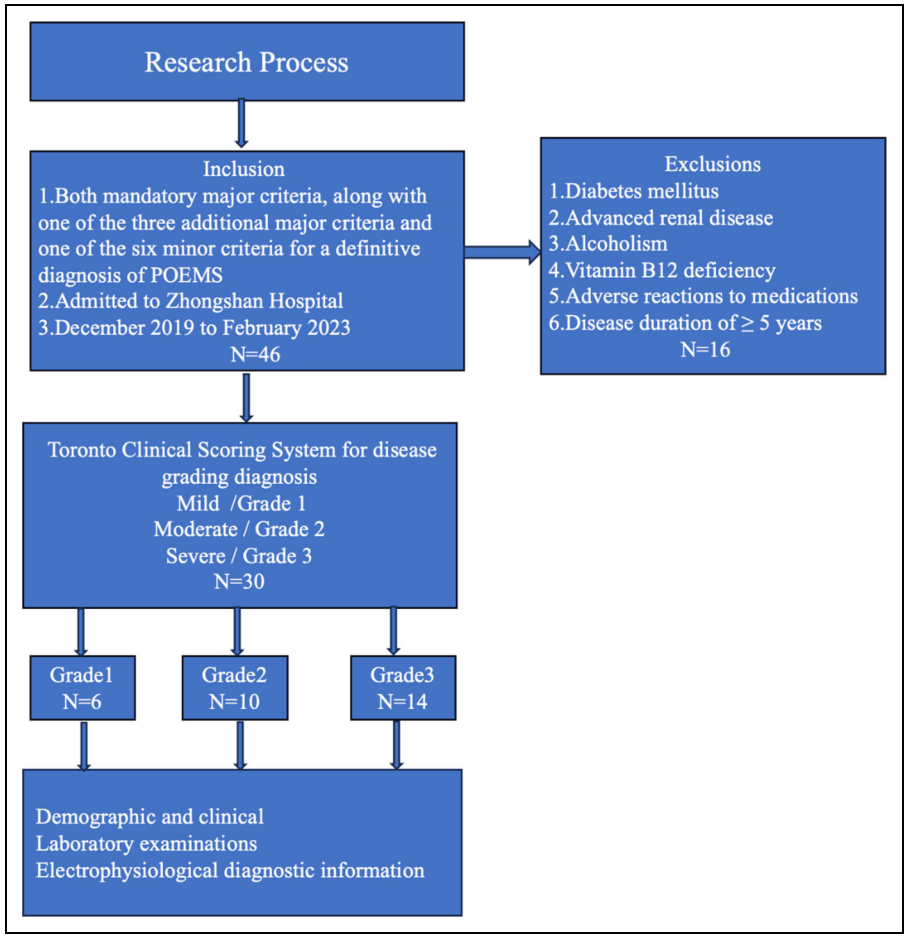

Figure 1. Selection of patients with POEMS, showing inclusion and exclusion criteria as well as subgroup assignment and patient numbers. POEMS: polyneuropathy, organmegaly, endocrinopathy, M-protein, skin changes syndrome.

duration, and the distribution of gender among the patients in the three groups did not show significant differences. VEGF levels exhibited an increasing trend with increasing grade, with average values of 343.0, 760.0, and 870.2 pg/ml, respectively. In grade 1 patients, limb involvement was evenly distributed, with 50% affecting both the upper and lower limbs. Among grade 2 patients, 50% experienced upper limb involvement, whereas in grade 3 patients, 57% had upper limb involvement. As the patients progressed to grades 2 and 3, 100% had lower limb involvement. The proportion of individuals experiencing involvement was 66.6%, 70%, and 57.1% in grades 1, 2, and 3, respectively. The clinical symptoms primarily related to motor impairment, which accounted for 33.3%, 30%, and 42.9% in grade 1, 2, and 3 respectively (Table 1).

Table 1. Clinical and electrophysiological characteristics of subjects analyzed in the study.

Variables	Grade 1	Grade 2	Grade 3
Patient count(n)	6	10	14
Age, years	58.8 ± 8.0	57.7 ± 9.8	53.3 ± 10.5
Gender (male)	3 (50.0%)	4 (40.0%)	6 (42.9%)
Duration, months	11.5 ± 7.2	18.2 ± 5.9	22.1 ± 16.7
With multiple myeloma	1 (16.7%)	4 (40.0%)	2 (14.3%)
With Castleman syndrome	2 (33.3%)	0	3 (21.4)
VEGF levels, pg/ml	343.0 (143.5–672.0)	760.0 (410.0–973.1)	870.2 (454.6–2440.0)
Electrophysiological findings			
Upper extremities involved	3 (50.0%)	5 (50.0%)	8 (57.1%)
Lower extremities involved	3 (50.0%)	10 (100.0%)	14 (100.0%)
Mainly sensory nerve involved	4 (66.6%)	7 (70.0%)	8 (57.1%)
Mainly motor nerve involved	2 (33.3%)	3 (30.0%)	6 (42.8%)

VEGF: vascular endothelial growth factor; *$p < 0.05$

Electrophysiological difference of different degrees of neuropathy

We measured and compared the amplitude and velocity of the motor and sensory nerves among the groups. The CMAP of the peroneal nerve decreased significantly with an increase in PN grade, the MCV of the peroneal nerve decreased significantly in grade 3 compared to grades 1 and 2 ($p < 0.0001$), and the MCV of the tibial nerve in grade 3 was significantly lower than that in grades 1 and 2 ($p < 0.0001$). The CMAP of the median nerve did not show a significant difference among the three groups; however, the MCV exhibited a significant decrease ($p = 0.0024$). In contrast, the CMAP of the ulnar nerve showed a significant decrease among the three groups, but the MCV did not show a significant difference. In the analysis of the sensory nerves, the SNAP of the sural nerve decreased significantly with an increase in the disease grade ($p = 0.0018$), and SCV of the sural nerve also decreased significantly with an increase in the disease grade ($p = 0.0029$), and the SNAP and SCV of the median and ulnar nerves showed no significant differences among the grading groups (Tables 2 and 3).

Analysis of risk factors for the degree of peripheral neuropathy in POEMS

According to correlation analysis between the degree of neuropathy and nerve NCS, changes in the NCS of multiple nerves can indicate the severity of neuropathy. The peroneal and sural nerves of the lower limbs were the most sensitive. To analyze the factors related to PN in the POEMS, we analyzed the linear correlation between age, disease course, VEGF, and the amplitude and conduction speed of the peroneal and sural nerves. Linear regression analysis showed a linear correlation between the CMAP of the peroneal nerve and the VEGF value. The SNCV of the ulnar nerve was significantly correlated with the course of the disease (Table 4).

Table 2. Comparison of amplitude and conduction velocity of motor nerves in different disease grades.

		Disease grade			
Motor nerve	NCS index	G1 (n = 6)	G2 (n = 10)	G3 (n = 14)	*p for trend*
Peroneal nerve	CMAP, mv	2.01 ± 2.17	1.22 ± 1.02	0.04 ± 0.16	**< 0.0001**
	MCV, m/s	19.87 ± 6.19	28.69 ± 5.88	1.68 ± 6.28	**< 0.0001**
Tibial nerve	CMAP, mv	1.45 ± 1.56	1.41 ± 1.94	0.08 ± 0.31	**< 0.0001**
	MCV, m/s	21.63 ± 4.75	28.94 ± 11.06	1.71 ± 6.39	**< 0.0001**
Median nerve	CMAP, mv	12.14 ± 3.68	9.68 ± 1.59	10.97 ± 5.28	0.2622
	MCV, m/s	31.73 ± 6.98	41.02 ± 5.81	27.43 ± 12.76	**0.0024**
Ulnar nerve	CMAP, mv	6.40 ± 4.30	6.91 ± 2.51	2.91 ± 2.03	**0.0036**
	MCV, m/s	33.23 ± 8.92	40.96 ± 7.58	28.37 ± 13.39	0.0187

NCS: nerve conduction studies; CMAP: compound motor active potentials; MCV: motor conduction velocity; G1: grade1; G2: grade2; G3: grade3. The bold *p*-values mean numerical value of $p < 0.05$.

Table 3. Comparison of amplitude and conduction velocity of sensory nerves in different disease grades.

		Disease grade			
Sensory nerve	EMG index	G1 (n = 6)	G2 (n = 10)	G3 (n = 14)	*p for trend*
Sural nerve	SNAP, μv	4.01 ± 1.83	3.96 ± 3.64	0.32 ± 0.86	**0.0018**
	SCV, m/s	36.38 ± 6.91	24.09 ± 17.00	4.99 ± 12.70	**0.0029**
Median nerve	SNAP, μv	9.90 ± 5.94	10.88 ± 9.13	5.58 ± 5.97	0.1596
	SCV, m/s	41.40 ± 7.76	38.52 ± 15.57	33.33 ± 19.63	0.5833
Ulnar nerve	SNAP, μv	6.65 ± 2.78	6.36 ± 5.93	4.43 ± 3.95	0.4160
	SCV, m/s	42.68 ± 5.91	33.83 ± 18.41	35.28 ± 17.34	0.7096

NCS: nerve conduction studies; SNAP: sensory nerve action potential; SCV: sensory conduction velocity; G1: grade1; G2: grade2; G3: grade3; EMG: electromyography. The bold *p*-values mean numerical value of $p < 0.05$.

Discussion

Main interpretations

Cardiological neurological diseases remain the main killer worldwide.[16–19] In a substantial sample of Chinese subjects with POEMS syndrome, the clinical characteristics revealed that males with the syndrome were twice as prevalent as female patients.[15] In contrast, we have more female patients than male patients in this study. Owing the study only recorded the patients who have completed neuroelectromyogram examination and small number of cases, this proportion has no special significance. As the neuropathy grade progressed, there was a notable shift from upper limb to lower limb involvement, with clinical symptoms related to motor impairment becoming more prevalent in higher grade patients. Therefore, lower limb motor symptoms may indicate severe PN. These 30 patients had varying degrees of motor and sensory defects in either a length-dependent

Table 4. Analysis of risk factors for the degree of peripheral neuropathy in POEMS.

Nerve	Parameters	Standard error	Standardized coefficients	*p*
Peroneal nerve CMAP	Course of NCS	0.007	0.511	0.084
	VEGF	0.000	1.114	**0.001**
	Age	0.037	0.607	0.066
Peroneal nerve MCV	Course of NCS	0.151	0.110	0.767
	VEGF	0.004	0.499	0.129
	Age	0.461	0.605	0.110
Sural nerve SNAP	Course of NCS	0.081	0.745	0.114
	VEGF	0.001	0.370	0.391
	Age	0.121	0.295	0.413
Sural nerve SCV	Course of NCS	0.342	0.813	**0.045**
	VEGF	0.005	0.270	0.421
	Age	0.507	0.221	0.441

NCS: nerve conduction studies; CMAP: compound motor active potentials; MCV: motor conduction velocity; SNAP: sensory nerve action potential; SCV: sensory conduction velocity; POEMS: polyneuropathy, organmegaly, endocrinopathy, M-protein, skin changes syndrome; VEGF: vascular endothelial growth factor. The bold *p*-values mean numerical value of $p < 0.05$.

pattern or polyradiculoneuropathy. Most of these are sensory defects that mainly involve the distal end of the lower limb. The patients mainly reported distal lower limb numbness and a few reported pain. A small number of patients reported limb weakness and motor impairment. Based on the subjective feelings of the patients' clinical symptoms, sensory deficits were greater than motor deficits in 19 patients, and lower limb abnormalities were the main symptoms in 27 patients.

The NCS data showed that the detection values for both motor and sensory functions in the lower limbs were more frequently abnormal than those in the upper limbs, which aligns with the clinical observation of more prevalent lower limb symptoms. Unexpected findings also emerged from the analysis of NCS in comparison with clinical symptoms. While most patients primarily complained of sensory nerve involvement, a subset exhibited more severe motor nerve damage, as evidenced by reduced amplitude and conduction velocity in the motor nerves. Furthermore, NCS indicated that the values for the motor nerves were more sensitive in grading the extent of nerve damage. Therefore, in patients with POEMS, neurophysiological data can complement aspects that may be overlooked by clinical symptoms. Furthermore, severe damage to lower limb motor nerve axons may be a crucial indicator of the exacerbation of PN in POEMS. According to the correlation analysis between the degree of neuropathy and the NCS results, changes in the NCS of multiple nerves can indicate the severity of neuropathy. The peroneal and sural nerves in the lower limbs exhibited the highest sensitivity, whereas the ulnar nerve in the upper limb was the most sensitive.

Analyzing risk factors not only aids in the diagnosis of POEMS but also provides insights into the prognosis of the syndrome and guides treatment strategies.[20] To analyze the factors related to PN in the POEMS, we analyzed the linear correlation between age, disease course, VEGF level, and the amplitude and conduction speed of the peroneal, sural, and ulnar nerves. Linear regression analysis showed a linear

correlation between the CMAP of the peroneal nerve and the VEGF value. The SCV of the ulnar nerve significantly correlated with the course of the disease. The elevated VEGF levels in our study suggest a correlation with the severity of PN. The diagnostic sensitivity for POEMS syndrome using elevated serum VEGF levels was 100% and the specificity was >90% (51%).[21] Conducting VEGF testing in individuals with acquired demyelinating neuropathy proves to be a cost-effective approach, facilitating early detection of POEMS and potentially enabling timely implementation of disease-specific treatments.[22,23] VEGF is used as a diagnostic criterion to distinguish POEMS syndrome from other PNs, and VEGF levels can also serve as an indicator for assessing the effectiveness of POEMS treatment.[24,25] These alterations might contribute to the development of POEMS by triggering vascular permeability and tissue edema.[26,27] Our regression analysis showed that the VEGF level demonstrated correlation with amplitude of the peroneal nerve, which was significant for our follow-up research. The relationship between VEGF and PN and whether the therapeutic effect is related to a decrease in VEGF levels deserve further comparative study.

The incidence of PN associated with POEMS syndrome in China has been documented at 99.49%.[14] The most common initial symptoms are limb numbness and/or weakness caused by PN. The sensorimotor polyneuropathy was the first symptom in 60.44% of Chinese patients. During the progression of the disease, PN was present in the remaining 39.5% of Chinese patients. Because the characteristics of PN combined with POEMS are easily confused with other PNs, and there is a lack of support for electromyographic diagnosis, misdiagnosis often occurs.[28] This, in turn, leads to a delayed diagnosis and additional clinical deterioration before an accurate diagnosis is established.[15] Our results suggest that the severity of PN increases with disease progression. Hence, it is essential to carefully monitor PN in suspected patients, whether it is an initial symptom. Timely neurophysiological assessments through NCSs are crucial, particularly when the clinical symptoms of PN are not yet pronounced during the initial phases of the condition.

Limitations

The study acknowledges a small sample size, potentially limiting the generalizability of the findings to a broader population. The study may lack comprehensive clinical data, such as comorbidities, medications, and lifestyle factors, which could potentially confound the observed associations. A more comprehensive assessment of patient characteristics could strengthen the study's findings. Although VEGF levels are discussed as a potential diagnostic and prognostic marker, the study doesn't delve into the limitations, sensitivity, and specificity of using VEGF in isolation. Future studies could explore the reliability of VEGF as a standalone biomarker. While the study notes a potential correlation between VEGF levels and PN severity, it doesn't extensively explore the therapeutic implications or whether interventions targeting VEGF could influence neuropathy outcomes. Further research in this area could provide valuable insights.

Conclusion

In conclusion, the electrophysiological findings demonstrated significant differences in motor and sensory nerve parameters with increasing neuropathy grade. Notably, the

peroneal and sural nerves of the lower limbs exhibited heightened sensitivity. These observations emphasize the significance of timely electrophysiological assessments and highlight the significance of VEGF levels and the disease course in predicting neuropathy severity, emphasizing the value of VEGF as a diagnostic and prognostic marker for POEMS syndrome.

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Author contributions statement

GN and YL wrote the main manuscript text. GN, ZZ, and SS prepared figures and tables. TL, YS, and JD revised the manuscript, proposed the idea, and supervised the whole study. All authors reviewed and approved the manuscript.

Consent for publication

Not applicable.

Data availability

The raw data are from https://www.jianguoyun.com/p/Dcw-Cj8QuaiFChjS8aoFIAA

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The study was approved by the Ethics Committee of Zhongshan Hospital Fudan University. Written consents were obtained from all the patients.

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Ethics declarations

The study was approved by the Ethics Committee of Zhongshan Hospital Fudan University (Ethical Approval Number: B2016-144R, Approval Date: 8 December 2016). Written consents were obtained from all the patients. We confirmed that all methods in our study were performed in accordance with the relevant guidelines and regulations.

ORCID iD

Yijun Shen https://orcid.org/0000-0002-6908-1334

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