Clinical and electrophysiological profiles in early recognition of polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes syndrome

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Abstract

Background: The detection of polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome at early stage is challenging for neurologists. Since polyneuropathy could be the first manifestation, it could be misdiagnosed as chronic inflammatory demyelinating polyneuropathy (CIDP). The present study aimed to determine the clinical and electrophysiological features of POEMS syndrome to distinguish from CIDP.

Methods: The data of a group of patients with POEMS (n=17) and patients with CIDP (n=17) in Zhongshan Hospital Fudan University from January 2015 to September 2017 were analyzed in this retrospective study. The clinical features, neurological symptoms, and electrophysiological findings were compared between the two groups.

Results: Clinically, patients with POEMS demonstrated significantly more neuropathic pain in the lower extremities than patients with CIDP (58.8% vs. 11.8%, P = 0.01). Multisystem features like edema, skin change, organomegaly, and thrombocytosis were also pointed towards the diagnosis of POEMS syndrome. Electrophysiologically, terminal latency index (TLI) was significantly higher in patients with POEMS than that in patients with CIDP (median nerve: 0.39 [0.17–0.52] vs. 0.30 [0.07–0.69], Z = –2.413, P = 0.016; ulnar nerve: 0.55 [0.23–0.78] vs. 0.42 [0.12–0.70], Z = –2.034, P = 0.042). Patients with POEMS demonstrated a higher frequency of absent compound muscle action potential of the tibial nerve (52.9% vs. 17.6%, P = 0.031), less conduction block (ulnar nerve: 0 vs. 35.3%, P = 0.018), and less temporal dispersion (median nerve: 17.6% vs. 58.8%, P = 0.032) than CIDP group. The combination of positive serum monoclonal protein and high TLI (if either one or both were present) discriminated POEMS from CIDP with a sensitivity of 94.1% and 47.1% and specificity of 76.5% and 100.0%, respectively.

Conclusions: POEMS syndrome could be distinguished from CIDP through typical clinical and electrophysiological characteristics in practice. The combination of serum monoclonal protein and high TLI might raise the sensitivity of detecting POEMS syndrome.

Keywords: Polyneuropathy; Organomegaly; Endocrinopathy; M protein and skin changes syndrome; Chronic inflammatory demyelinating polyradiculoneuropathy; Terminal latency index

Introduction

Polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome is a paraneoplastic syndrome due to an underlying plasma cell neoplasm.¹²³ Polyneuropathy is usually the dominant and sometimes the first chief complaint of patients with POEMS syndrome, prompting consultation with neurology specialists. The pattern of neuropathy of POEMS syndrome is symmetrical sensory motor polyneuropathy and radiculoneuropathy and the electrophysiological studies often showed demyelinating features, which mimic the most common acquired demyelinating neuropathy-chronic inflammatory demyelinating polyradiculo-neuropathy (CIDP). The treatments of the two diseases are completely different.¹²³ If misdiagnosed as CIDP, the specific treatment for POEMS syndrome may be postponed, thereby exacerbating the condition. For acquired demyelinating polyneuropathy, serum immunofixation electrophoresis is the first study to identify the presence of a monoclonal gammopathy.⁴ If IgG or IgA monoclonal gammopathy is found, vascular endothelial growth factor (VEGF) assays, skeletal surveys, and bone marrow biopsy should be conducted. However, in practice, some patients with POEMS syndrome showed a negative serum immunofixation electrophoresis result at their first visit. Nonetheless, if each patient with acquired demyelinating polyneuropathy underwent a thorough examination, it would cause a high medical cost. This led us to identify the
specific pattern of clinical features and nerve conduction study results in POEMS syndrome and to discuss its role in distinguishing the two diseases at the early stage.

Therefore, we summarized the clinical manifestations and electrophysiological characteristics of a group of patients with POEMS syndrome from January 2015 to September 2017 in Zhongshan Hospital Fudan University, Shanghai, China and compared them to a group of patients with CIDP diagnosed in the same period. We analyzed the diagnostic threshold of common clinical and electrophysiological characteristics of POEMS syndrome which can aid the neurologists in recognizing and diagnosing this syndrome.

Methods

Ethical approval

The study was approved by the Ethics Committee of Zhongshan Hospital Fudan University. Informed consents were obtained from all the patients.

Participants

This retrospective observational study was conducted in a University-Affiliated hospital. A total of 17 consecutive patients with POEMS syndrome were included between January 2015 and September 2017. All patients fulfilled the diagnostic criteria of POEMS syndrome and were diagnosed by hematologists. The major criteria for the syndrome were polyneuropathy, clonal plasma cell disorder (PCD), sclerotic bone lesions, elevated VEGF, and the presence of Castleman disease. Minor features included organomegaly, endocrinopathy, characteristic skin changes, papilledema, extra-vascular volume overload (edema or ascites), and thrombocytosis. The diagnosis was based on three of the major criteria, two of which must include polyneuropathy and clonal PCD, and at least one of the minor criteria.[5] Also, 17 patients with CIDP were enrolled in the same study period. The diagnosis of CIDP fulfilled the diagnostic criteria for definite CIDP according to 2010 European Federation of Neurological Societies/Peripheral Nerve Society guideline.[5] Briefly, the criteria include clinically progressive, stepwise or recurrent symmetric motor weakness and sensory dysfunction of all extremities, developed over at least 2 months. In addition, the cranial nerve may be affected, and tendon reflexes may be absent or reduced in all extremities; these findings were supported by electrodiagnostic criteria, cerebrospinal fluid (CSF) results, magnetic resonance imaging (MRI), nerve biopsy, or treatment response. The diagnosis of CIDP was made by two expert neurologists.

Clinical manifestations and electrophysiological findings

Demographic characteristics (age, gender, height, and weight), internal medical findings (such as skin change, edema, and organomegaly), neurological manifestations (such as muscle weakness, loss of sensory, or neuropathic pain) were compared between POEMS syndrome and CIDP groups.

Data of neurophysiological tests were gathered from all participants to identify the electrophysiological characteristics of POEMS syndrome. A Medoc electroneurogram and electromyography system (Medoc Company, Israel) was used to perform nerve conduction tests. Sural sensory, superficial peroneal sensory, tibial motor, and peroneal motor nerve conduction tests were performed in the lower extremities while ulnar sensory, median sensory, ulnar motor, and median motor nerve conduction tests were performed in the upper extremities. Also, needle electromyography was performed in the chosen muscles of the upper and lower extremities.

Terminal latency index (TLI) was used to compare the conduction slowing in the distal and intermediate segments of the median and ulnar nerves, which was calculated using the following formula: TLI = terminal distance (mm)/(distal latency [ms] × conduction velocity [m/s]). The normal range of TLI was 0.20 to 0.40 for the median nerve and 0.29 to 0.49 for the ulnar nerve.[6] Conduction block was defined as a ≥50% change in amplitude proximal: distal; temporal irrespective of the distance. Distal compound muscle action potential (CMAP) had to be ≥1 mV. Temporal dispersion was defined as the duration of the distal potential/duration of the proximal potential <0.7. In order to evaluate the extent of length-dependent axon degeneration, tibial/median CMAP amplitude ratio was calculated.

Statistical analysis

Data are presented as number (%), median (range), or mean ± standard deviation. The differences between continuous valuables were analyzed using the Mann-Whitney U test. The differences in the categorical variables were compared using the Fisher exact test. A P value of less than 0.05 was considered to be statistically significant. SPSS (version 13.0, IBM Corporation, Somers, NY, USA) was used for statistical analysis.

Results

Demographic characteristics of the patients

Demographic parameters showed that gender, age, height, and weight were similar between POEMS syndrome and CIDP groups [Table 1]. The time course from the onset of the disease to administration was also similar in both groups (6 [2–25]) vs. 3 [1–24] months, Z = -1.696, P = 0.09). Two patients in CIDP group received steroid treatment before enrolling to the study while other patients in both groups did not undergo specific disease-modifying treatment.

Clinical characteristics

All patients with POEMS syndrome had peripheral neuropathy and plasma cell proliferative disorder. Although all of the patients with POEMS syndrome presented clonal plasma cell proliferative disorder, only 11 (64.7%) patients showed a positive result of serum immunofixation electrophoresis (IgA or IgG gammanopathy) results for...
experienced neuropathic pain in the lower extremities and weakness in the lower and upper extremities. Both groups showed progressive symmetric numbness. With respect to the neurological signs and symptoms, both POEMS syndrome group and CIDP group showed frequency of edema, skin changes, organomegaly, thrombocytosis, and ataxia. The ultrasound findings were also performed in patients with CIDP. The frequency of edema, skin changes, organomegaly, thrombocytosis, and ataxia was similar between the two groups, while tremor was significantly more patients with POEMS syndrome than CIDP patients (58.8% vs. 11.8%, P = 0.010). In POEMS syndrome, neuropathic pain was mostly located in the distal lower limbs, following a length-dependent pattern. Pricking pain, burning pain, squeezing pain, or pressure pain was described by patients with POEMS syndrome. Conversely, a majority of the patients with CIDP suffered from insensate neuropathy. Only two patients described pain in both the upper and lower limbs, not with length dependent pattern. The frequency of ataxia was similar between the two groups, while tremor was reported only in two patients with CIDP [Table 1].

### Electrophysiological features

The electrophysiological parameters were summarized in Tables 2 and 3. Both of the two groups demonstrated demyelinating features in the motor nerves-prolonged distal motor latency (DML), reduced motor conduction velocity, and prolonged F wave latency. The rate of apparently prolonged DML (>200% upper limit of the normal values [ULN]) was lower in POEMS syndrome group than that in CIDP group (median nerve: 0.39 [0.17–0.52] vs. 0.30 [0.07–0.69], Z = −2.413, P = 0.016; ulnar nerve: 0.55 [0.23–0.78] vs. 0.42 [0.12–0.70], Z = −2.034,

### Table 1: Demographic data and neurological features of POEMS syndrome and CIDP.

| Variables                  | POEMS syndrome (n = 17) | CIDP (n = 17) | t value | P value |
|----------------------------|-------------------------|---------------|---------|---------|
| Age (years)                | 57.59 ± 9.10            | 51.88 ± 17.42 | 1.197   | 0.240   |
| Gender (male)              | 7 (41.2)                | 10 (58.8)     | NA      | 0.490   |
| Height (cm)                | 162.59 ± 7.54           | 165.17 ± 9.13 | −0.901  | 0.374   |
| Weight (kg)                | 64.23 ± 8.43            | 65.06 ± 8.74  | −0.279  | 0.782   |
| BMI (kg/m²)                | 24.20 ± 1.58            | 23.71 ± 1.22  | −0.962  | 0.343   |
| With diabetes              | 1 (5.9)                 | 2 (11.8)      | NA      | 1.000   |
| With hypothyroidism        | 9 (52.9)                | 2 (11.8)      | NA      | 0.026   |
| Signs and symptoms         |                         |               |         |         |
| Skin change                | 13 (76.5)               | 1 (5.9)       | NA      | <0.001* |
| Edema                      | 14 (82.4)               | 1 (5.9)       | NA      | <0.001* |
| Weakness                   |                         |               |         |         |
| Upper extremities          | 8 (42.1)                | 9 (52.9)      | NA      | 1.000   |
| Lower extremities          | 11 (64.7)               | 14 (82.4)     | NA      | 0.438   |
| Numbness                   |                         |               |         |         |
| Upper extremities          | 13 (76.5)               | 10 (58.8)     | NA      | 0.465   |
| Lower extremities          | 17 (100.0)              | 15 (88.2)     | NA      | 0.485   |
| Neuropathic pain           |                         |               |         |         |
| White blood                | 3 (17.6)                | 2 (11.8)      | NA      | 1.000   |
| Lower extremities          | 10 (58.8)               | 2 (11.8)      | NA      | 0.010   |
| Ataxia                     | 3 (17.6)                | 5 (29.4)      | NA      | 0.688   |
| Tremor                     | 0                      | 1 (5.9)       | NA      | 0.485   |
| Laboratory findings        |                         |               |         |         |
| Serum monoclonal protein   | 11 (64.7)               | 0             | NA      | <0.001* |
| Thrombocytosis             | 7 (41.2)                | 0             | NA      | <0.001* |
| Ultrasound findings        |                         |               |         |         |
| Hepatosplenomegaly         | 14 (82.4)               | 0             | NA      | <0.001* |
| Ascites                    | 9 (52.9)                | 0             | NA      | <0.001* |

Data are presented as n (%) or mean ± standard deviation. *P < 0.05. POEMS: Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; CIDP: Chronic inflammatory demyelinating polyneuropathy; BMI: Body mass index; NA: Not applicable.

Note: The table includes demographic data and neurological features of POEMS syndrome and CIDP, with comparisons between the two groups. The data are presented as counts or percentages, and statistical significance is indicated where appropriate.
P = 0.042), which indicated that POEMS syndrome had more predominant demyelination in the intermediate segment than that in the distal part. Compared with the CIDP group, patients with POEMS syndrome demonstrated a higher frequency of absent CMAP of the tibial nerve. The tibial/median CMAP amplitude ratio was significantly smaller for patients with POEMS syndrome compared with the patients with CIDP (0 [0.1–10.4] vs. 0.20 [0–1.64], Z = −2.853, P = 0.049), indicating a marked axonal loss in the lower extremities in POEMS syndrome. Conduction block and temporal dispersion were less frequent in POEMS syndrome group than that in CIDP group (ulnar nerve conduction block: 0 vs. 35.3%, P = 0.018; median nerve temporal dispersion: 17.6% vs. 58.8%, P = 0.032) [Table 2]. For sensory nerve conduction, patients with POEMS syndrome showed a reduced sensory conduction velocity in the upper extremities (median nerve: 40.0 [31.0–53.8] vs. 47.7 [39.4–62.2], Z = −2.772, P = 0.006; ulnar nerve: 38.3 [27.8–49.6] vs. 43.6 [32.9–56.9], Z = −1.985, P = 0.047). More than half of the patients in both groups showed absent SNAPs in the lower extremities. The reduction of SNAPs was similar in both groups [Table 3].

Table 2: Motor nerve conduction data for patients with POEMS syndrome and CIDP.

| Variables          | POEMS syndrome (n = 17) | CIDP (n = 17) | Z value | P value |
|--------------------|-------------------------|--------------|---------|---------|
| Median nerve       |                         |              |         |         |
| DML                |                         |              |         |         |
| Value (ms)         | 5.6 (3.6–13.2)          | 9.2 (2.8–21.2) | −1.119  | 0.263   |
| >200% ULN          | 1 (5.9)                 | 9 (52.9)     | NA      | 0.007†  |
| MCV (m/s)          | 32.9 (17.7–45.7)        | 33.2 (16.6–52.3) | −0.258  | 0.796   |
| F latency (s)      | 40.3 (32.7–55.2)        | 39.8 (27.4–68.1) | −0.044  | 0.965   |
| TLI                |                         |              |         |         |
| Value              | 0.39 (0.17–0.52)        | 0.30 (0.07–0.69) | −2.413  | 0.016†  |
| >ULN               | 9 (52.9)                | 2 (11.8)     | NA      | 0.026‡  |
| cMAP (mV)          | 5.7 (0.1–10.4)          | 6.7 (0.3–13.1) | −0.482  | 0.65    |
| Conduction block   | 0                      | 4 (23.5)     | NA      | 0.103   |
| Temporal dispersion| 3 (17.6)                | 10 (58.8)    | NA      | 0.032‡  |
| Ulnar nerve        |                         |              |         |         |
| DML                |                         |              |         |         |
| Value (ms)         | 3.7 (2.8–6.7)           | 4.9 (2.3–13.9) | −1.705  | 0.088   |
| >200% ULN          | 1 (5.9)                 | 8 (47.1)     | NA      | 0.017†  |
| MCV (m/s)          | 33.5 (16.4–49.6)        | 33.7 (13.1–64.8) | −0.189  | 0.850   |
| F latency (s)      | 39.3 (32.4–58.4)        | 39.3 (27.8–59.2) | −0.631  | 0.528   |
| TLI                |                         |              |         |         |
| Value              | 0.55 (0.23–0.78)        | 0.42 (0.12–0.70) | −2.034  | 0.042†  |
| >ULN               | 12 (70.6)               | 4 (23.5)     | NA      | 0.015‡  |
| cMAP (mV)          | 5.8 (0.3–13.6)          | 4.6 (0.02–12.1) | −0.293  | 0.770   |
| Conduction block   | 0                      | 6 (35.3)     | NA      | 0.018†  |
| Temporal dispersion| 3 (17.6)                | 9 (51.9)     | NA      | 0.071   |
| Tibial nerve       |                         |              |         |         |
| No potential       | 9 (52.9)                | 3 (17.6)     | NA      | 0.031‡  |
| DML                |                         |              |         |         |
| Value (ms)         | 6.2 (4.6–8.0)           | 7.6 (3.5–19.6) | −0.956  | 0.339   |
| >150% ULN (%)      | 0                      | 5 (37.5)     | NA      | 0.115   |
| MCV (m/s)          | 24.5 (19.3–36.5)        | 31.5 (9.8–45.6) | −1.263  | 0.297   |
| cMAP (mV)          | 0 (0–6.7)               | 2.7 (0–15.6)  | −2.219  | 0.026†  |
| Conduction block   | 1 (12.5)                | 4 (28.6)     | NA      | 0.613   |
| Temporal dispersion| 2 (25.0)                | 8 (57.1)     | NA      | 0.204   |
| Tibial/median cMAP ratio | 0 (0–1.43) | 0.20 (0–1.64) | −2.853  | 0.049†  |
| Peroneal nerve     |                         |              |         |         |
| No potential       | 6 (35.3)                | 5 (29.4)     | NA      | 1.000   |
| DML                |                         |              |         |         |
| Value (ms)         | 5.4 (4.1–7.4)           | 7.1 (3.5–25.7) | −0.862  | 0.389   |
| >150% ULN (%)      | 0                      | 5 (41.7)     | NA      | 0.037†  |
| MCV (m/s)          | 26.4 (18.7–42.3)        | 35.3 (20.4–48.2) | −1.785  | 0.074   |
| cMAP (mV)          | 0.4 (0–4.9)             | 1.4 (0–11.7)  | −0.543  | 0.587   |
| Conduction block   | 0                      | 4 (33.3)     | NA      | 0.093   |
| Temporal dispersion| 1 (9.1)                 | 7 (58.3)     | NA      | 0.027‡  |

Data are presented as n (%), median (range). *P < 0.05. POEMS: Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; CIDP: Chronic inflammatory demyelinating polyneuropathy; DML: Distal motor latency; MCV: Motor conduction velocity; TLI: Terminal latency index; ULN: Upper limit of the normal values; cMAP: Compound muscle action potential; NA: Not applicable.
Preliminary diagnostic applications

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the positive serum monoclonal protein and high TLI are shown in Table 4. TLI that exceeded the ULN of the median or ulnar nerve was defined as high TLI. The combination of positive serum monoclonal protein and high TLI (if either one or both were present) discriminated POEMS syndrome from CIDP with a sensitivity of 94.1% and 47.1% and specificity of 76.5% and 100.0%, respectively. The other clinical features of POEMS syndrome included length-dependent neuropathic pain, edema, skin change, and thrombocytosis, which were all distinguishing characteristics. These features should be considered as diagnostic clues at the first visit of the patient with demyelinating neuropathy.

As demonstrated previously, the neuropathy of POEMS syndrome was a symmetrical sensorimotor polyradiculoneuropathy. A majority of the patients followed a length-dependent pattern of polyneuropathy with steady progressive numbness and weakness which began in the lower extremities.[7-9] The frequency of neuropathic pain was significantly higher in POEMS syndrome group than that in CIDP group.[7] It has been reported that neuropathic pain was frequently experienced in patients with POEMS syndrome and was closely related to a reduction in the myelinated, but not unmyelinated fiber population.[10] Conversely, patients with CIDP demonstrated more objective symptoms and signs. Some patients might report non-specific muscle soreness, but few reported neuropathic pain.[11]

The electrophysiological features of POEMS syndrome patients in our group were similar to those reported

Discussion

The current study demonstrated the clinical and electrophysiological characteristics of POEMS syndrome, and discussed their value to distinguish POEMS syndrome from CIDP at the first visit. The electrophysiological features of POEMS syndrome were as followings: (1) high TLI indicated more severe demyelination in the intermediate segment than that in the distal part; (2) reduced tibial/median CMAP amplitude ratio indicated length-dependent axonal loss; (3) less conduction block and temporal disperse indicated more uniform demyelination than CIDP. The combination of positive serum monoclonal protein and high TLI (if either one or both were present) discriminated POEMS syndrome from CIDP with a sensitivity of 94.1% and 47.1% and specificity of 76.5% and 100.0%, respectively. The other clinical features of POEMS syndrome included length-dependent neuropathic pain, edema, skin change, and thrombocytosis, which were all distinguishing characteristics. These features should be considered as diagnostic clues at the first visit of the patient with demyelinating neuropathy.
In conclusion, POEMS syndrome should be considered in patients with neuropathic pain, especially in the lower extremities and also in patients with polyradiculoneuropathy accompanying edema, characteristic skin lesion, thrombocytosis, or organomegaly. The electrophysiological characteristics supporting POEMS syndrome included higher TLI, less conduction block and temporal disperse, and more obvious length-dependent axonal degeneration compared to CIDP. The combination of serum monoclonal protein and high TLI might raise the sensitivity in detecting POEMS syndrome.

Conflicts of interest
None.

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How to cite this article: Wang Q, Liu P, Ji LL, Wu S, Feng GD, Wang X, Dong JH. Clinical and electrophysiological profiles in early recognition of polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes syndrome. Chin Med J 2019;132:1666–1672. doi: 10.1097/CM9.000000000000318