Clinical Neurophysiology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Altered axonal excitability properties and nerve edema in POEMS syndrome

Satsuki Mitsuma, Sonoko Misawa, Kazumoto Shibuya, Sagiri Isose, Yukari Sekiguchi, Yuta Iwai, Minako Beppu, Keisuke Watanabe, Hiroshi Amino, Satoshi Kuwabara *

Department of Neurology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan

ARTICLE INFO

Article history:
Accepted 15 January 2015
Available online xxxx

Keywords:
POEMS syndrome
Axonal excitability
Nerve ultrasound
Ion channel

HIGHLIGHTS

- Axonal excitability and its correlation with serum VEGF and nerve edema detected by ultrasound were studied in POEMS syndrome.
- Excitability testing suggested possibly altered sodium, potassium, and inward rectifying currents, some of which were correlated with VEGF levels and nerve edema.
- In addition to structural changes (demyelination), nerve edema induced by upregulated VEGF, and upregulated inflammatory cytokines can modulate profiles of POEMS neuropathy.

ABSTRACT

Objective: POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is a rare cause of demyelinating neuropathy with upregulation of vascular endothelial growth factor (VEGF). This study aimed to elucidate axonal excitability properties and their relation to VEGF levels and nerve edema in POEMS neuropathy.
Methods: Axonal excitability measurement and nerve ultrasound were performed in the median nerve of 33 patients with POEMS syndrome. Serum VEGF levels were measured by ELISA.
Results: Compared with normal subjects ($n = 87$), POEMS patients showed longer strength-duration time constant, fanning-out of threshold electrotonus curves, and greater threshold changes in a hyperpolarizing current–threshold relationship. Nerve ultrasound showed significant enlargement in POEMS patients. Serum VEGF levels and the extent of nerve edema partly correlated with nerve conduction slowing, as well as persistent sodium currents and inward rectification.
Conclusions: In POEMS syndrome, patterns of changes in excitability properties could suggest increased persistent sodium currents, and impaired potassium and inward rectifying channels. The findings were not consistent with depolarization due to nerve edema and compression ischemia.
Significance: In addition to demyelination, nerve edema induced by upregulated VEGF, and upregulated inflammatory cytokines could modulate profiles of POEMS neuropathy.

1. Introduction

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is a rare cause of demyelinating polyneuropathy associated with monoclonal plasma cell proliferation and multi-organ involvement (Bardwick et al., 1980; Kuwabara et al., 2008a; Dispenzieri, 2014). Serum levels of vascular endothelial growth factor (VEGF) are markedly increased in POEMS syndrome, and increased vascular permeability and neovascularization mediated by VEGF are likely to cause characteristic symptoms such as edema, pleural effusion/ascites, organomegaly and skin angiomata (Watanabe et al., 1996). However, mechanisms for neuropathy in POEMS syndrome have not yet been elucidated, whereas pathological studies have shown perineurial edema, and segmental demyelination with uncompacted myelin and secondary axonal degeneration (Kanda, 2013).

The proposed mechanisms for POEMS neuropathy include that the combination of blood-nerve barrier breakdown by VEGF and following invasion of other inflammatory cytokines such as

* Corresponding author. Tel.: +81 43 222 7171x5414; fax: +81 43 226 2160.
E-mail address: kuwabara-s@faculty.chiba-u.jp (S. Kuwabara).

http://dx.doi.org/10.1016/j.clinph.2015.01.018
1388-2457/

interleukin-12, and tumor necrosis-α causes nerve demyelination (Kanai et al., 2012), and that nerve edema mediated by VEGF leads to compression ischemia and axonal depolarization (Kanda, 2013), but these hypotheses still need confirmation.

Axonal excitability testing using threshold tracking was developed to investigate ion channel function, membrane potential, and passive membrane properties of human axons *in vivo* (Bostock et al., 1998; Burke et al., 2001), and over the past two decades, the technique has been extensively applied to the study of the biophysical properties of human peripheral nerves and have provided important insights into axonal ion channel function in health and disease (Nodera and Kaji, 2006; Sawai et al., 2008).

Separately, nerve ultrasound is also becoming increasingly important in the diagnosis and evaluation of peripheral neuropathies particularly in the 2000's (Padua et al., 2012) providing new insights into macroscopic nerve morphology. In this study, we aimed to elucidate axonal excitability properties and their relation to nerve morphology and serum VEGF levels in patients with POEMS syndrome.

2. Methods

2.1. Subjects

This study prospectively enrolled 33 consecutive patients (25 men; age range 36–75 years, mean 55 years) with newly diagnosed POEMS syndrome, who fulfilled published criteria (Kuwabara et al., 2008a) seen at a single tertiary hospital (Chiba University Hospital) in Japan from January 2012 to September 2014. We excluded patients with renal failure because serum K^+ levels can significantly alter membrane potential and axonal excitability properties (Kiernan et al., 2000).

Normal control data for axonal excitability testing were obtained from 87 age-matched healthy subjects (49 men; age range 38–76 years, mean 56 years). Serum VEGF levels were measured by ELISA commercially (Special Reference Laboratory Co. Ltd., Tokyo, Japan). All the patients and normal control subjects gave informed consent to the study procedures, which was approved by the Ethics Committee of Chiba University Graduate School of Medicine.

2.2. Neurophysiological assessment

Neurophysiological evaluation was performed before thalidomide treatment, and in 9 patients, follow-up studies were done 3 months later. Nerve conduction studies were conducted using conventional procedures and a standard electromyography machine (Viking 4, Nicolet Biomedical Japan, Tokyo, Japan). Nerve excitability testing was performed on the median nerve at the wrist (3 cm proximal to the wrist crease) using a computerized program (QTRAC® with multiple excitability protocol, TRONDNF, Institute of Neurology, London, UK) as described previously (Kiernan et al., 2000; Nasu et al., 2014). Compound muscle action potentials (CMAPs) were recorded from the abductor pollicis brevis. Skin temperature was measured near the stimulating site and maintained above 32.0 °C (using extra heating, if necessary). Excitability indices included strength-duration time constant, threshold electrotonus, and refractoriness, supernormality, and late subnormality of the recovery cycle of axonal excitability with a single supramaximal conditioning stimulus, and a current–threshold relationship.

2.3. Nerve ultrasound

Ultrasound examination was performed with Logiq E9 (GE Healthcare Japan, Tokyo, Japan) with a 6–12 MHz electronic linear array probe at the wrist, forearm, and elbow portion of the median nerve trunk. Cross-sectional area were measured at the inner border of the thin hyperechoic epineural rim by the continuous tracing technique and the average values were calculated after serially measuring three times (Kerasnoudis et al., 2014). No additional force was applied other than the weight of the transducer and the extremities were kept in the neutral position to avoid causing any artificial nerve deformity.

2.4. Statistical analysis

All statistical tests were two-sided. The comparison of paired parameters of nerve conduction studies or excitability testing between baseline and the second examination was evaluated via the paired *t*-test with Bonferroni's correction for multiple testing. Regression analysis was performed by Pearson's correlation coefficient test. All statistical analyses were performed using JMP software, version 5.1.1 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Nerve excitability testing and ultrasound

Table 1 shows results of nerve conduction studies, and excitability testing. Nerve conduction velocities were significantly slowed consistent with primary demyelinating neuropathy. In excitability testing, strength-duration time constant was significantly longer and current required for produce 50% of the maximal CMAP was greater for POEMS patients than for normal controls. In the recovery cycle of axonal excitability, POEMS patients had greater superexcitability and smaller late subexcitability. POEMS patients showed fanning-out in threshold electrotonus particularly in the hyperpolarizing direction, and greater threshold changes to hyperpolarizing currents in current–threshold relationships (Fig. 1).

Nerve ultrasonography showed significantly greater cross-sectional area at the wrist, forearm, and elbow portion of the median nerve in patients with POEMS syndrome than in normal subjects.

3.2. Correlation with serum VEGF levels and nerve enlargement

Before treatment, serum VEGF levels were greatly increased in all patients with POEMS syndrome; the mean value was 5143 pg/ml (normal < 1000 pg/ml), ranging from 1080 to 16,400 pg/ml. Table 2 shows correlation of electrophysiological indices with serum VEGF levels and cross-sectional area at the elbow. Higher serum VEGF levels were associated with longer distal motor latency, and smaller CMAP amplitude in nerve conduction studies, and greater threshold changes to long hyperpolarizing conditioning currents.

Separately larger cross-sectional area on nerve ultrasound was associated with slower nerve conduction velocity, smaller CMAP amplitude, and loner strength-duration time constant. Serum VEGF levels and nerve cross-sectional area at the time of examination did not show significant correlation.

3.3. Serial changes after treatment

Sequential examinations on nerve excitability and ultrasound were performed before and 3 months after thalidomide treatment in 9 patients. Table 3 shows serial changes. Serum VEGF levels decreased. Nerve cross-sectional area significantly reduced after treatment, suggesting edema was a major cause of nerve enlargement. Significant improvement was observed in distal latency in nerve conduction studies. In excitability testing, superexcitability

Please cite this article in press as: Mitsuma S et al. Altered axonal excitability properties and nerve edema in POEMS syndrome. Clin Neurophysiol (2015), http://dx.doi.org/10.1016/j.clinph.2015.01.018