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Clinical Short Communication

A significant correlation between cauda equina conduction time and cerebrospinal fluid protein in chronic inflammatory demyelinating polyradiculoneuropathy

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ABSTRACT

We investigated the relationship between the involvement of the cauda equina in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and the increment of cerebrospinal fluid (CSF) protein. We measured cauda equina conduction time (CECT) in 14 CIDP patients using magnetic stimulation with a MATS coil. Statistical analysis revealed that CECT and CSF protein had a significant positive linear correlation. Conduction time of the peripheral nerve trunk, in contrast, had no significant linear correlation with CSF protein. We revealed that the involvement of the cauda equina and increment of CSF protein are closely related. In CIDP cases with elevated CSF protein, spinal nerves including the cauda equina are very likely involved.

1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated disorder commonly presenting with muscular weakness of limbs, distal dominant sensory disturbance, and hyporeflexia [1]. From results acquired using a flat, round 20-cm diameter coil, named Magnetic Augmented Translumbosacral Stimulation (MATS) coil for magnetic stimulation, we previously reported that the cauda equina is much more frequently physiologically involved in CIDP than the peripheral nerve trunk is [2]. This “MATS coil stimulation” technique enables us to measure cauda equina conduction time (CECT) by activating the most proximal and most distal sites of the cauda equina [3–6]. The prominent cauda equina involvement might be explained by two anatomical features of the cauda equina, i.e. its lack of the blood-nerve barrier and its direct exposure to cerebrospinal fluid (CSF). These characteristics might enable unidentified antibodies or other circulating factors to access the cauda equina directly [2]. Given these results, we could expect that the involvement of the cauda equina and increment of CSF protein may be closely related. To our knowledge, however, this expectation has not been tested in an investigation.

In this paper, we demonstrated a significant linear correlation between CECT and CSF protein. The conduction time of the peripheral nerve trunk, in contrast, had no significant correlation with CSF protein. Therefore, the involvement of the cauda equina is closely related to increment of CSF protein in CIDP.

2. Methods

We studied 14 CIDP patients (8 males and 6 females) whose diagnoses had been made according to the established diagnostic criteria [1]. The age of the patients was 56.6 ± 15.1 years (mean ± standard deviation). Most of these patients were included in our previously published paper [2]. Patients with other factors possibly affecting CSF protein level such as cervical myelopathy were excluded. None of the patients had CSF pleocytosis. The characteristics of the CIDP patients are summarized in Table 1. Twelve patients fulfilled the electrodiagnostic criteria for definite CIDP and two patients for possible CIDP (cases 4 and 5). The two patients were temporarily improved by immunomodulatory treatments, although their symptoms deteriorated after the treatments. Finally, they fulfilled the electrodiagnostic criteria for definite CIDP. All of the patients had sensory disturbances. Normal values were made from 20 age-matched healthy subjects (mean ±

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Table 1
Characteristics of and results from 14 CIDP patients.

Case No.	Age	Sex	Disease duration	Hughes Scales	Electrodiagnostic criteria	CECT (ms)	S1-Knee CT (ms)	Knee-Ankle CT (ms)	CSF protein (mg/dL)
1	63	F	3 months	1	Definite	5.1	10.5	9.3	46↑
2	42	M	6 months	3	Definite	5.1	10.6	8.3	46↑
3	61	M	6 months	2	Definite	7.1↑	11.8↑	9.2	67↑
4	51	M	7 months	1	Possible	3.8	11.3	7.6	51↑
5	33	F	1 year	2	Possible	6.9↑	12.7↑	7.2	32
6	57	F	1 year	2	Definite	10.1↑	11.7↑	7.6	71↑
7	71	M	1 year	2	Definite	9.1↑	15.5↑	9.4	74↑
8	54	M	3.5 years	2	Definite	5.8↑	10.7	11.2↑	45
9	26	F	5 years	1	Definite	10.3↑	14.6↑	11.1↑	59↑
10	57	M	7 years	2	Definite	5.9↑	12.2↑	10.1↑	43
11	66	F	11 years	2	Definite	7.1↑	17.7↑	8.4	61↑
12	65	M	15 years	2	Definite	5.8↑	9.7	7.8	40
13	63	F	24 years	4	Definite	8.1↑	11.8↑	11.1↑	80↑
14	83	M	29 years	4	Definite	6.8↑	10.8	7.4	65↑
Normal values (mean ± SD, n = 20 subjects)						3.7 ± 0.8	9.2 ± 1.0	7.2 ± 0.9	
Mean + 2.5SD (upper limit of normal values)						< 5.7	< 11.7	< 9.5	< 46

CECT: cauda equina conduction time, S1-Knee CT: S1-Knee conduction time, Knee-Ankle CT: Knee-Ankle conduction time.
CSF: cerebrospinal fluid, SD: standard deviation.
Hughes functional grading scale: grade 1 = minimal signs and symptoms and able to run, grade 2 = ambulates independently, grade 3 = able to walk 5 m with aid, grade 4 = bound to bed.

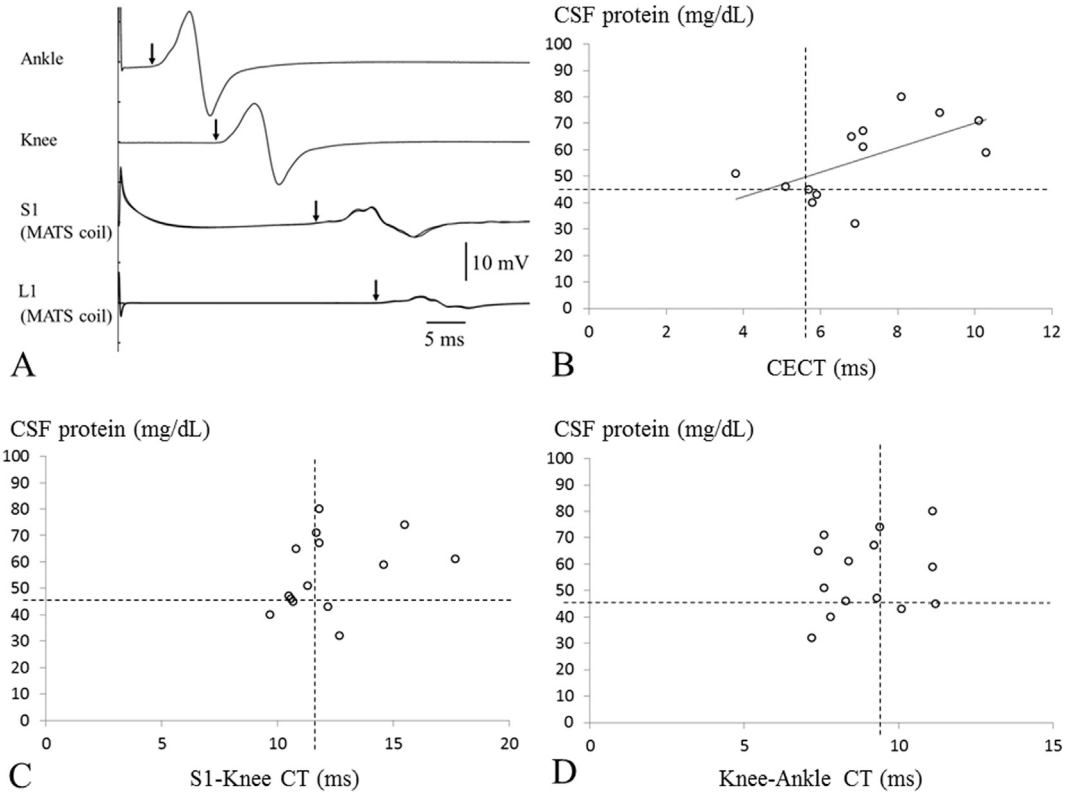

Fig. 1. MATS coil stimulation and correlation analysis.
A: MATS coil stimulation. CECT is calculated as the latency difference between the L1 and S1 levels. S1-Knee CT is calculated as the latency difference between the S1 level and the knee. Knee-Ankle CT is calculated as the latency difference between the knee and ankle (modified from Matsumoto et al., 2010, with permission). B: Correlation between CECT and CSF protein. Solid line shows a significant linear correlation (P = 0.022, R = 0.603). C: Correlation between S1-Knee CT and CSF protein. There is no significant linear correlation (P = 0.238). D: Correlation between Knee-Ankle CT and CSF protein. There is no significant linear correlation (P = 0.424). Dashed lines show the upper limits of normal values.
CECT: cauda equina conduction time, CSF: cerebrospinal fluid, S1-Knee CT: S1-Knee conduction time, Knee-Ankle CT: Knee-Ankle conduction time.

standard deviation: 52.1 ± 12.2 years).

The stimulation methods have been described previously [2]. Briefly, compound muscle action potentials (CMAPs) were recorded from the abductor hallucis muscle on the more strongly affected side. Filters were set between 20 Hz and 3 kHz and signals were amplified and recorded by a computer (Neuropack MEB-2306; Nihon Kohden Corporation, Tokyo, Japan). To measure Knee-Ankle conduction time (Knee-Ankle CT), the tibial nerve was supramaximally stimulated at the ankle and knee using a conventional electrical stimulator (Neuropack MEB-2306; Nihon Kohden Corporation, Tokyo, Japan). To measure CECT and S1-Knee conduction time (S1-Knee CT), the cauda equina was stimulated at its most distal site (S1 level) and its most proximal site (L1 level) using a monophasic stimulator (Magstim 200^2, The Magstim Co. Ltd., Whitland, UK) and a powerful round coil (MATS coil, The Magstim

Co. Ltd.). To measure onset latency of CMAPs at the most distal cauda equina (S1 level), stimulus intensity was gradually increased. If possible, supramaximal CMAPs were obtained, and if impossible, reproducible CMAPs were obtained. We judged that supramaximal stimulation was achieved only when the size of superimposed CMAPs was saturated before the stimulus intensity reached maximal stimulator output. To measure onset latency of CMAPs at the distal cauda equina (L1 level), stimulus intensity was gradually increased, and reproducible CMAPs were obtained. Supramaximal CMAPs were usually unobtainable at this site, which prevented us from judging whether there was conduction block within the cauda equina. S1 level and L1 level latencies were stable even in submaximal stimulations, because the fastest motor fibers are preferentially activated in magnetic stimulation at these sites [5,6]. Onset latency was measured by at least two neurophysiologists. The frequency of prolongation of CECT was statistically compared with that of Knee-Ankle CT using Wilcoxon's signed rank test.

To investigate the relationship between CECT and CSF protein, a simple linear regression analysis was performed. Similarly, we analyzed the relationships of S1-Knee CT and Knee-Ankle CT to CSF protein. The coefficient of correlation was expressed as R. P values < 0.05 were considered statistically significant. Statistical analysis was conducted using SPSS software (SPSS, ver. 16.0; SPSS Inc., Chicago, IL, USA).

Informed consent to participate in this study was obtained from all subjects. The protocol was approved by the Ethics Committee of the University of Tokyo (No. 1983). The experiments were conducted in accordance with the ethical standards of the Declaration of Helsinki.

3. Results

Fig. 1A shows CMAPs in a representative CIDP patient (case 5). Although the Knee-Ankle CT obtained by ankle and knee stimulations was normal (7.2 ms), CECT obtained by S1- and L1-level MATS coil stimulation was prolonged (6.9 ms, upper limit of normal values is 5.7 ms). S1-Knee CT was also prolonged (12.7 ms, upper limit of normal values is 11.7 ms) and conduction block between S1 level and knee was present. All of the patients fulfilled the criteria for definite CIDP. The results from all patients are summarized in Table 1. CECT was prolonged in 11 patients (78.6%). Knee-Ankle CT was prolonged in only four patients (28.6%). The prolongation of CECT was observed at a significantly higher frequency than was that of Knee-Ankle CT ($P = 0.009$). Ten patients had increment of CSF protein (71.4%). CECT and CSF protein had a significant positive linear correlation ($P = 0.022$, $R = 0.603$, Fig. 1B). Between S1-Knee CT or Knee-Ankle CT and CSF protein, on the other hand, there was no significant linear correlation (S1-Knee CT: $P = 0.238$, Fig. 1C; Knee-Ankle CT: $P = 0.424$, Fig. 1D).

4. Discussion

We demonstrated a significant linear correlation between CECT and CSF protein in CIDP for the first time. We also showed that the conduction time of the peripheral nerve trunk (S1-Knee CT or Knee-Ankle CT) had no significant linear correlation with CSF protein. These results suggest that the involvement of the cauda equina is closely related to the increment of CSF protein. Furthermore, as we have previously reported [2], although the cauda equina is only half as long as the peripheral nerve from the knee to the ankle, prolongation of CECT was observed more frequently than was that of Knee-Ankle CT. On the basis of the anatomical differences between the cauda equina and the peripheral nerve trunk, the preferential involvement of the cauda equina is likely to be due to the cauda equina's lack of the blood-nerve barrier and its direct exposure to CSF. Taken together, our results demonstrate that the cauda equina is much more frequently involved in CIDP than the peripheral nerve trunk is, and that the involvement of the cauda equina is closely related to increment of CSF protein.

We speculate that several mechanisms contribute to the close pathophysiological relationship between the involvement of the cauda equina and increment of CSF protein. First, unidentified antibodies and other circulating factors might be present in CSF, primarily causing CSF protein to increase. Second, the breakdown of the myelin sheath of the cauda equina might cause the increment of CSF protein. Third, both primary and secondary mechanisms might contribute to this pathophysiological relationship. To reveal the details of the relationship, further investigations into the components of CSF protein must be undertaken.

Prior studies of magnetic resonance imaging of peripheral nerves in CIDP showed the nerve root hypertrophy was frequently observed [7,8]. The relationship between the imaging findings and CSF protein may be useful to verify our results, i.e. the involvement of the cauda equina and increment of CSF protein. Such imaging investigations also must be undertaken.

We have confirmed that the involvement of the cauda equina and increment of CSF protein are closely related. Therefore, in CIDP cases with elevated CSF protein, we should consider that spinal nerves including the cauda equina are likely to be involved.

Conflict of interest statement

The authors have no potential conflicts of interest.

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References

[1] P.Y. Van den Bergh, R.D. Hadden, P. Bouche, D.R. Cornblath, A. Hahn, I. Illa, et al., European federation of neurological societies/peripheral nerve society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the peripheral nerve society - first revision, Eur. J. Neurol. 17 (2010) 356–363.

[2] H. Matsumoto, R. Hanajima, Y. Terao, A. Yugeta, M. Hamada, Y. Shirota, et al., Prominent cauda equina involvement in the patients with chronic inflammatory demyelinating polyradiculoneuropathy, J. Neurol. Sci. 290 (2010) 112–114.

[3] H. Matsumoto, F. Octaviana, R. Hanajima, Y. Terao, A. Yugeta, M. Hamada, et al., Magnetic lumbosacral motor root stimulation with a flat, large round coil, Clin. Neurophysiol. 120 (2009) 770–775.

[4] H. Matsumoto, F. Octaviana, Y. Terao, R. Hanajima, A. Yugeta, M. Hamada, et al., Magnetic stimulation of the cauda equina in the spinal canal with a flat, large round coil, J. Neurol. Sci. 284 (2009) 46–51.

[5] H. Matsumoto, R. Hanajima, Y. Terao, Y. Ugawa, Magnetic-motor-root stimulation: review, Clin. Neurophysiol. 124 (2013) 1055–1167.

[6] P.M. Rossini, D. Burke, R. Chen, L.G. Cohen, Z. Daskalakis, R. Di Iorio, et al., Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee, Clin. Neurophysiol. 126 (2015) 1071–1107.

[7] R.N. De Silva, H.J. Willison, D. Doyle, A.I. Weir, D.M. Hadley, A.M. Thomas, Nerve root hypertrophy in chronic inflammatory demyelinating polyneuropathy, Muscle Nerve 17 (1994) 168–170.

[8] S. Kuwabara, M. Nakajima, S. Matsuda, T. Hattori, Magnetic resonance imaging at the demyelinative foci in chronic inflammatory demyelinating polyneuropathy, Neurology 48 (1997) 874–877.