Electrophysiological demyelinating features in hereditary ATTR amyloidosis

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Abstract

Objective: To elucidate the electrophysiological demyelinating features in patients with hereditary ATTR amyloidosis that may lead to a misdiagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP).

Methods: In 102 patients with hereditary ATTR amyloidosis (85 Val30Met and 17 non-Val30Met; 37 and 65 from endemic and non-endemic areas, respectively), results of motor nerve conduction studies (MNCSs) with a 2-Hz low-cut filter in the unilateral ulnar and tibial nerves were retrospectively investigated to assess whether each MNCS parameter demonstrated demyelinating features that fulfill the European Federation of Neurological Societies/Peripheral Nerve Society electrodiagnostic (EFNS/PNS EDX) criteria for CIDP.

Results: Thirteen patients with low compound muscle action potential (CMAP) amplitude in the tibial nerve (0.7 ± 0.7 mV) and prolonged distal CMAP duration in the ulnar nerve satisfied the definite EFNS/PNS EDX criteria for CIDP. Abnormal temporal dispersion and prolongation of distal latency in the tibial nerve were observed in 5 of 13 patients. However, only one of 13 patients presented with reduction of motor conduction velocity in each nerve. No patient exhibited conduction block in any nerve.

Conclusion: Patients with hereditary ATTR amyloidosis occasionally show electrophysiological demyelinating features without conduction block following severe axonal degeneration.

Keywords: Hereditary ATTR amyloidosis, transthyretin familial amyloid polyneuropathy, CIDP, EFNS/PNS electrodiagnostic criteria, electrophysiological demyelination, axonal degeneration, nerve conduction study

1. Introduction

Hereditary ATTR amyloidosis, also known as transthyretin (TTR) familial amyloid polyneuropathy, is an inherited fatal disease induced by systemic deposition of TTR [1, 2]. Most patients with hereditary ATTR amyloidosis show progressive axonal polyneuropathy [3]. As strategic treatments, including liver transplantation, the TTR stabilizer, and gene silencing therapy are being established, early diagnosis of hereditary ATTR amyloidosis becomes extremely important [4-6]. Nevertheless, a proportion of hereditary ATTR amyloidosis patients with Val30Met (p.Val50Met) from non-endemic areas and those with non-Val30Met are misdiagnosed with other neuropathies, especially chronic inflammatory demyelinating polyneuropathy (CIDP) [7-9]. Clinical factors contributing to misdiagnosis include lack of familial history, nonspecific sensory and motor neuropathy, slight dysautonomia, and slight cardiac symptoms [10].

To discriminate hereditary ATTR amyloidosis from CIDP, electrophysiological approaches should be helpful as the predominant feature is axonal degeneration in the former and demyelination in the latter. However, few studies have been conducted on electrophysiological demyelinating features in hereditary ATTR amyloidosis mimicking CIDP using the European Federation of Neurological Societies/Peripheral Nerve Society electrodiagnostic (EFNS/PNS EDX) criteria, the gold standard criteria of CIDP

[11]. Mariani et al. [12] demonstrated that 52 of 160 (33%) patients with hereditary ATTR amyloidosis fulfilled the definite EFNS/PNS EDX criteria for CIDP by performing electrophysiological studies on four limbs. The ratio of patients with electrophysiological demyelination was greater in patients with Val30Met from non-endemic areas and Ile107Val (p.Ile127Val) than in those with Val30Met from endemic areas and Ser77Thr (p.Ser97Thr). Cortese et al. [13] reported that 7 of 19 (37%) patients with hereditary ATTR amyloidosis from non-endemic areas, who were initially misdiagnosed with CIDP, satisfied the definite EFNS/PNS EDX criteria due to reduced motor conduction velocities (MCVs) with decreased compound muscle action potential (CMAP) amplitudes. Recently, Lozeron et al. [14] demonstrated that prolongation of distal latency (DL) in the median nerve under severe reduced CMAP amplitudes in the upper and lower limbs is a frequent demyelinating feature in hereditary ATTR amyloidosis patients adhering to the EFNS/PNS criteria. However, these studies did not discuss other parameters of motor nerve conduction studies (MNCSs) in detail. To reduce electrophysiological misinterpretation of patients with hereditary ATTR amyloidosis as those with CIDP, detailed investigation into electrophysiological demyelinating features in the former is needed. This study aimed to elucidate electrophysiological demyelinating features that fulfill the EFNS/PNS EDX

criteria for CIDP in hereditary ATTR amyloidosis by analyzing each MNCS parameter precisely.

2. Methods

Patients

Clinical and electrophysiological data were retrospectively collected from patients with hereditary ATTR amyloidosis referred to Shinshu University Hospital between January 2003 and December 2016. In all patients, diagnosis of hereditary ATTR amyloidosis was confirmed by TTR-derived amyloid deposition in biopsy specimens and identification of disease-causing mutations in the *TTR* gene. All patients revealed at least one neuropathic manifestation, including polyneuropathy, carpal tunnel syndrome, or autonomic neuropathy. Autonomic neuropathy was defined as having orthostatic hypotension, dysuria, alternating bowel movement abnormalities, or impotence. Patients with other causes of sensorimotor neuropathy or prior treatments such as TTR stabilizers and liver transplantation were excluded. A total of 102 hereditary ATTR amyloidosis patients were enrolled. All of 37 patients with Val30Met from endemic areas originated from Ogawa village, except for one patient from the Arao district. A proportion of these patients were included in a previous study [15].

Table 1 shows a summary of the clinical background of the patients. This retrospective study was approved by the Committee for Medical Ethics of Shinshu University School of Medicine (approval number: 3622). Informed consent was obtained in the form of opt-out on the website.

Electrophysiological assessment

MNCSs were performed using the belly–tendon method in one-sided ulnar and tibial nerves 1 month to 11 years (mean 3.2 ± 2.3 years) after first neuropathic manifestations. All MNCSs were performed in our institution using MEB2200 (Nihon-Koden, Tokyo, Japan) between January 2003 and August 2009 or MEB2312 (Nihon-Koden, Tokyo, Japan) between September 2009 and December 2016. Low- and high-cut filter settings were set at 2 Hz and 10 kHz, respectively. Skin temperature of the examined segment was maintained ≥30 °C throughout the examination. When skin temperature decreased to that below 30 °C, the limbs were warmed using an electric heating blanket. CMAPs in the ulnar and tibial nerves were recorded from the abductor digiti minimi and abductor hallucis muscles, respectively. Electrodes were placed for electrical stimulation 7 cm proximal from the active electrode and below the elbow for the ulnar nerve and 10 cm proximal from the active electrode and popliteal fossa in the

tibial nerve. CMAP amplitude, DL, MCV, F-wave latency and persistence, and distal CMAP duration were measured. CMAP amplitude was defined as baseline to negative peak amplitude. Distal CMAP duration was defined as the period from rising of the first negative phase to return to baseline of the last negative phase. F-wave was elicited by 10 stimulations. Latency was measured as the onset time of the first deflection from baseline. According to the EFNS/PNS EDX criteria, the absence of the F-wave was defined as the disappearance of the F-wave with distal CMAP amplitude ≥20% of the normal value. Conduction block and abnormal temporal dispersion were confirmed as ≥50% CMAP amplitude reduction with the distal CMAP amplitude over 20% of the normal value and ≥30% CMAP duration increase between the proximal and distal CMAP amplitudes, respectively [11]. Normal values of CMAP amplitude, DL, MCV, and F-wave latency were determined based on the MNCSs of 25 healthy volunteers aged between 21 to 59 years (mean, 35.2 ± 13.8 years). All examinations were performed with close attention using the same protocol. Because the EFNS/PNS EDX criteria for CIDP are constituted of MNCS parameters only and findings of sensory nerve conduction studies are included in the supportive criteria, we focused on results of MNCS only. Sensory nerve action potentials (SNAPs) severely decrease or disappear from the initial stage in hereditary ATTR amyloidosis [15, 16], and thus, analysis of

sensory nerve conduction study findings including sensory conduction velocities is often difficult especially in the legs. Indeed, SNAPs of the tibial and sural nerves disappeared in 31/69 and 32/94 of patients, respectively.

Analysis

To evaluate demyelination characteristics, each MNCS parameter was analyzed according to the EFNS/PNS EDX criteria for CIDP. To reveal the effects of the severity of axonal degeneration on demyelinating features, the correlations between CMAP amplitude and other MNCS parameters including DL, MCV, F-wave latency, and distal CMAP duration were analyzed using Spearman rank correlation coefficient. As for distal CMAP duration, the EFNS/PNS EDX criteria defines the cut-off value using only a low-cut filter setting of 20 Hz [11, 17]. Although low-cut filter settings strongly influence distal CMAP duration [18, 19], this issue is not usually noticeable. When a low-cut filter setting of lower frequency is used, recorded CMAP waveform includes lower frequency components. Hence, the lower the low-cut filter setting, the longer the distal CMAP duration. Thus, we evaluated the duration using the EFNS/PNS EDX criteria and the upper value in the low-cut filter setting of 2 Hz recently proposed by Mitsuma et al. [19]. The background of patients with hereditary ATTR amyloidosis who

satisfied the definite EFNS/PNS EDX criteria for CIDP was assessed. Differences between two groups were analyzed using Mann–Whitney U test or Fisher's exact test. *p* values of <0.05 were considered statistically significant. Statistical analysis was performed using Bell Curve for Excel (Social Survey Research Information Co., Ltd, Japan).

3. Results

Electrophysiological demyelinating features in hereditary ATTR amyloidosis

Table 2 shows the baseline electrophysiological characteristics. Compared with patients from endemic areas, those from non-endemic areas showed significantly reduced CMAP amplitude and slowed MCV in both the nerves. There were no differences in baseline electrophysiological features between patients with Val30Met and non-V30Met (data not shown). Table 3 summarizes demyelinating parameters that meet the EFNS/PNS EDX criteria for CIDP. Notably, many of the patients showed the prolongation of distal CMAP duration in the ulnar nerve. DL prolongation and abnormal temporal dispersion in the tibial nerve were observed in 10 % of patients. MCV reduction was equally rare, and conduction block was not observed in any nerve. F-wave abnormality only affected the ulnar nerve. This may be because the F-waves of

the tibial nerve were diminished in 22 patients with reduced CMAP amplitude (under 20% of normal value). As a result, a total of 13 and 7 patients satisfied definite or possible EDX criteria for CIDP, respectively. No patients fulfilled probable criteria. Due to disappearance of CMAP, analyses of the other parameters in the tibial nerve were not conducted in 13 patients. Because of severely decreased CMAP amplitudes, examinations of the F-wave in the ulnar and tibial nerves were not performed in 5 and 6 patients, respectively. One patient was excluded from analysis of distal CMAP duration and temporal dispersion in the ulnar nerve due to lack of raw CMAP waveform data. Furthermore, one patient was excluded from analysis of temporal dispersion in the tibial nerve because CMAP disappeared following proximal stimulation. Table 4 shows the abnormal demyelinating parameters that meet the EFNS/PNS EDX criteria in each hereditary ATTR amyloidosis patient fulfilling the definite criteria. All of these 13 patients showed severe decrease of CMAP amplitude in the tibial nerve (0.7 ± 0.7 mV) and prolongation of distal CMAP duration in the ulnar nerve under EFNS/PNS EDX criteria.

Effects of axonal degeneration on demyelinating features

Figure 1 and 2 show the correlations between CMAP amplitude and the other

four MNCS parameters (DL, MCV, F-wave latency, and distal CMAP duration) in the ulnar and tibial nerves, respectively. A significant negative correlation was found between CMAP amplitude and DL in the ulnar (r_s = -0.58, p <0.001) and tibial nerves (r_s = -0.63, p <0.001). Conversely, a significant positive correlation was found between CMAP amplitude and MCV in the ulnar (r_s = 0.64, p <0.001) and tibial nerves (r_s = 0.64, p <0.001). Especially in the tibial nerve, prolongation of DL and slowing of MCV were evident under severe axonal degeneration (CMAP amplitude less than 1 mV). F-wave latency was negatively correlated with CMAP amplitude in the ulnar (r_s = -0.55, p <0.001) and tibial nerves (r_s = -0.61, p <0.001). A weak positive correlation was found between CMAP amplitude and distal CMAP duration in the tibial (r_s = 0.27, p <0.05) but not in the ulnar nerve (r_s = -0.07, p = 0.49). Although CMAP in the ulnar nerve was detected in all patients, CMAP in the tibial nerve was absent in 12 patients.

Effects of a low-cut filter setting on distal CMAP duration

Prolongation of the distal CMAP duration in the ulnar nerve using the upper value of the EFNS/PNS EDX criteria was found in 45 patients (Table 3, Figure 1D). The number dramatically decreased to only two patients when we used the upper value of the low-cut filter setting of 2 Hz based on the recommendations by Mitsuma et al. [19].

By using the value proposed by Mitsuma et al. [19], ten of 13 patients with definite EFNS/PNS EDX criteria were downgraded as those with possible CIDP. In contrast to the ulnar nerve, little difference between the two criteria was seen in the tibial nerve (Table 3, Figure 2D).

Background of patients with the definite EFNS/PNS EDX criteria

Table 5 shows comparison between hereditary ATTR amyloidosis patients with and without definite EFNS/PNS EDX criteria for CIDP. There were no differences in clinical background between two groups. All of 13 patients with definite EFNS/PNS EDX criteria showed length-dependent polyneuropathy; the distribution of neuropathy was similar to that of atypical CIDP such as distal acquired demyelinating symmetric (DADS) rather than that of typical CIDP with proximal and distal weakness in all limbs. Furthermore, all of 13 patients did not have some of the clinical red-flags of hereditary ATTR amyloidosis (10 patients from non-endemic areas, 6 without family history, 11 without dissociated sensory disturbances, 3 without apparent dysautonomia, and 11 without apparent cardiac symptoms, 12 without carpal tunnel syndrome). Indeed, one of 13 patients with definite EFNS/PNS EDX criteria was initially diagnosed with CIDP and treated with intravenous immunoglobulin.

4. Discussion

In the present study, of the 102 patients with hereditary ATTR amyloidosis, 13 patients fulfilled the definite EFNS/PNS EDX criteria for CIDP. Factors contributing to electrophysiological demyelination included severe axonal degeneration and interpretation of distal CMAP duration without considering low-cut filter settings. No patients showed conduction block.

DL, MCV, and F-wave latency

DL, MCV, and F-wave latency are indices reflecting the function of the fastest motor fiber. These parameters deteriorated with a decrease in CMAP amplitude (Figure 1, 2). Elongation of DL, slowing of MCV, and prolonged F-wave latency with CMAP reduction have been observed in axonal neuropathy and motor neuron disease, likely due to the loss of large myelinated fibers and secondary demyelination [20, 21]. Indeed, large myelinated fiber loss with segmental demyelination was reported in patients with hereditary ATTR amyloidosis [22, 23]. Compared with DL, the abnormality of MCV in the tibial nerve was not evident in the present study in contrast to the findings by Cortese et al. [13]. Our results may reflect the more severe nerve damage in the nerve

terminals than the nerve trunk under length-dependent axonal degeneration.

Distal CMAP duration

Under the EFNS/PNS EDX criteria, 45 of 102 patients showed prolongation of distal CMAP duration, an index of heterogeneous demyelination at the distal nerve terminals, in the ulnar nerve. However, this striking finding is highly likely due to the effect of low-cut filter setting of 2 Hz in our study but not due to true heterogeneous demyelination. The cut-off of distal CMAP duration in the EFNS/PNS EDX criteria was defined using a low-cut filter of 20 Hz [11, 17]. However, a low-cut filter adopts different settings (2 to 20 Hz) in different institutions. Low-cut filter settings strongly influence distal CMAP duration, and thus, Mitsuma et al. [19] provided new cut-off values based on each nerve and low-cut filter settings that could clearly differentiate CIDP from diabetic polyneuropathy. When applying this upper value of 9.6 ms for the ulnar nerve in a 2-Hz low-cut filter to our case series, the number of patients who showed prolongation of distal CMAP duration dramatically decreased. This diagnostic discrepancy derives from the substantial difference of 2.9 ms between these cut-off values. This was not true for the tibial nerve because of a minor difference (0.4 ms) between the two cut-off values. Our results support the usefulness of cut-off values

derived with each low-cut filter setting to discriminate axonal neuropathies from demyelinating ones, especially in the ulnar nerve. The revision of cut-off values of DCMAP duration based on each low-cut filter setting in the new EDX criteria or the global unification of filter settings would be required.

Abnormal temporal dispersion and conduction block

Abnormal temporal dispersion and conduction block are crucial indices of heterogeneous demyelination in intermediate nerve trunks. Abnormal temporal dispersion, often associated with CMAP reduction (3.3 ± 5.2 mV), was noticeable predominantly in the tibial nerve. However, abnormal temporal dispersion in the tibial nerve (36.6 ± 6.2%) slightly exceeded the upper threshold set to 30% increments of CMAP duration. This mild abnormal temporal dispersion may be due to the following reason: MNCS in the tibial nerve physiologically exhibits temporal dispersion due to CMAP recording from multiple intrinsic muscles of the foot and a wider distance between stimulation and recording sites [24].

No patient showed conduction blocks in both nerves in the present study. Indeed, reported cases with conduction block are extremely rare in patients with hereditary ATTR amyloidosis [25]. Patients with acute axonal neuropathies such as

vasculitic neuropathy and acute motor axonal neuropathy sometimes show findings similar to conduction block [26, 27]. The pathophysiology is presumed to be due to nerve ischemia and nodal axonal dysfunction. In contrast, hereditary ATTR amyloidosis is a disease with gradual loss of fibers. Conduction block is a finding contradictory to hereditary ATTR amyloidosis.

Hereditary ATTR amyloidosis electrophysiologically mimicking CIDP

Our study showed that patients with hereditary ATTR amyloidosis occasionally present with electrophysiological demyelinating features under severe axonal degeneration, and patients from non-endemic areas had significantly reduced CMAP amplitudes and MCVs (Table 2). Consistent with our results, Koike et al. demonstrated that reductions of CMAP amplitude and MCV were more profound in the late-onset cases from non-endemic areas than in the early-onset cases from endemic areas [16]. Their pathological investigation showed abundant axonal sprouting and small amounts of re- and de-myelination with severely decreased large myelinated fibers in some of the late-onset cases from non-endemic areas [16, 22]. Lozeron et al. [13] also demonstrated that approximately half of the 13 sporadic hereditary ATTR amyloidosis patients from non-endemic areas with definite EFNS/PNS EDX criteria present with pathological

demyelinating features. Furthermore, ten of these 13 patients had axonal degeneration with CMAP amplitude less than 5.4 mV in the ulnar nerve. Indeed, ten of the 13 patients with the definite EFNS/PNS EDX criteria in our study met this CMAP amplitude value in the ulnar nerve (Table 4). Therefore, we expected that more patients from non-endemic areas would satisfy the definite EFNS/PNS EDX criteria. However, there were no significant differences in clinical backgrounds including endemic/non-endemic area between patients with and without the definite EFNS/PNS EDX criteria (Table 5). We assumed that this discrepancy is due to both fewer tested nerves in our study and severe decrease or disappearance of CMAPs in patients from non-endemic areas (Table 2). To fulfill the definite EFNS/PNS EDX criteria, two nerves with one of each demyelinating parameter are usually needed [11]. Fewer examined nerves in our study would also contribute to lower rate of patients with the definite EFNS/PNS EDX criteria compared to that of other studies [12, 13]. In our opinion, and as described in another study [12], patients from non-endemic areas tend to fulfill the definite EFNS/PNS EDX criteria with severe axonal degeneration rather than those from endemic areas if we perform MNCS at 4 nerves (median, ulnar, peroneal, and tibial nerves) and additional bilateral examinations as per the EFNS/PNS guideline [11].

Limitations

Our study has several limitations including retrospective analysis of unilateral MNCSs in the unilateral ulnar and tibial nerves with a low-cut filter setting of 2 Hz. We did not compare the electrophysiological and histopathological findings because 45 patients were transferred from other institutions after obtaining a confirmed diagnosis, and we prefer abdominal fat or gastroduodenal biopsy rather than nerve biopsy to detect amyloid depositions due to its convenience and less-invasiveness [28, 29]. Furthermore, MNCSs of several transferred patients were not the first electrophysiological examination that was performed. This time gap between the first recordings taken and our recordings may have contributed to the progression of axonal degeneration and exaggerated the demyelinating features in our study. Finally, a validation study on the effects of low-cut filter settings on distal CMAP duration is also needed because other studies in patients with hereditary ATTR amyloidosis did not include the low-cut filter setting using electrophysiological assessment and details on the effects of the filter setting.

Conclusions

Our study revealed the electrophysiological demyelinating features in

hereditary ATTR amyloidosis using the EFNS/PNS EDX criteria. Under severe axonal degeneration, patients with hereditary ATTR amyloidosis occasionally show electrophysiological demyelinating features without conduction block. To reduce electrophysiological misinterpretation of hereditary ATTR amyloidosis as CIDP, we recommend careful evaluation of demyelinating features with severely decreased CMAP amplitude in patients with length-dependent polyneuropathy. Moreover, analysis of distal CMAP duration based on low-cut filter settings would be essential to minimize electrophysiological misinterpretation.

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Disclosure of interest

The authors report no conflict of interest.

Abbreviations

CIDP: chronic inflammatory demyelinating polyneuropathy

CMAP: compound action muscle potential

DADS: distal acquired demyelinating symmetric

DL: distal latency

EDX: electrodiagnostic

EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society

MCV: motor conduction velocity

MNCS: motor nerve conduction study

SNAP: sensory nerve action potential

TTR: transthyretin

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Figure legends

Figure 1. Effects of axonal degeneration on demyelinating features in the ulnar nerve

DL (**A**) and F-wave latency (**C**) prolong with decline in CMAP amplitude. MCV (**B**) reduces with decrease in CMAP amplitude. No correlation between CMAP amplitude and distal CMAP duration is observed (**D**). Each mark represents patients from endemic areas (filled circles) and from non-endemic areas (white circles). Lower or upper thresholds in our facility are indicated by dashed lines. Diagnostic thresholds in the EFNS/PNS criteria are indicated by solid lines. Dotted lines only in distal CMAP duration indicate the upper value of the low-cut filter setting of 2 Hz proposed by Mitsuma et al. [19].

Figure 2. Effects of axonal degeneration on demyelinating features in the tibial nerve

DL (**A**) and F-wave latency (**C**) prolong with decline in CMAP amplitude. MCV (**B**) reduces with decrease in CMAP amplitude. No correlation between CMAP amplitude and distal CMAP duration is observed (**D**). Each mark represents patients from endemic areas (filled circles) and from non-endemic areas (white circles). Lower or upper thresholds in our facility are indicated by dashed lines. Diagnostic thresholds in the EFNS/PNS criteria are indicated by solid lines. Dotted lines only in distal CMAP duration indicate the upper value of the low-cut filter setting of 2 Hz proposed by Mitsuma et al. [19].

Table 1 Clinical background

	Patients from endemic areas n = 37	Patients from non-endemic areas n = 65	Differences between patients from endemic and non-endemic areas
Women/men	17/20	18/47	$p = 0.08$
TTR mutation			
Val30Met/non-Val30Met*	37/0	48/17	$p < 0.01$§
Presence of family history	37	39	$p < 0.01$§
Age of neurological onset (years)	33.3 ± 8.3	56.4 ± 15.0	$p < 0.01$‖
Duration from neurological onset to electrophysiological study (years)	2.8 ± 1.9	3.4 ± 2.5	$p = 0.33$
Clinical stage†			
Stage 0/I/II/III	3/29/5/0	4/52/7/2	

Initial manifestation			
Polyneuropathy	25	47	$p = 0.66$
Carpal tunnel syndrome	0	6	$p = 0.08$
Autonomic neuropathy	11	5	$p < 0.01$[§]
Other symptoms[‡]	1	7	$p = 0.25$

Each value is expressed as numbers of patients or mean ± SD.

* 3 Ser50Arg (p.Ser70Arg), 2 Asp38Ala (p.Asp58Ala), 2 Phe44Ser (p.Phe64Ser), 2 Thr60Ala(p.Thr80Ala), 2 Gly42Arg (p.Gly62Arg), 1 Glu42Gly (p.Glu62Gly), 1 Arg54Thr (p.Arg74Thr), 1 Ile107Val (p.Ile127Val), 1 Ile84Asn (p.Ile104Asn), 1 Ser50Ile (p.Ser70Ile), 1 Tyr114His (p.Tyr134His).

[†] Clinical stages of hereditary ATTR amyloidosis as defined by Countinho et al [30].

Stage 0: patients have some autonomic dysfunction but lack polyneuropathic symptoms or signs,

stage I: polyneuropathy is localized to lower limbs, and patients can walk without help,

stage II: polyneuropathy involves upper and lower limbs; patients are handicapped but can still walk with help,

stage III: severe polyneuropathy and autonomic dysfunction confines patients to wheelchair, or they are bedridden.

[‡] Cardiac and eye involvement; heart failure, arrhythmia, vitreous opacity, glaucoma.

[§]Statistically significant difference after Fisher's exact test.

[I] Statistically significant difference after Mann-Whitney U test.

Table 2 Electrophysiological parameters

	Patients from endemic areas	Patients from non-endemic areas	Normal value	EFNS/PNS demyelination value*	Mitsuma's value†	Differences between patients from endemic and non-endemic areas
Ulnar nerve						
CMAP amplitude (mV)	7.4 ± 3.0	5.4 ± 3.4	> 5.5			$p < 0.01$§
CMAP amplitude ≤ 1.0 mV (n)	1	5				$p = 0.41$
DL (ms)	3.1 ± 0.5	3.2 ± 0.6	< 3.1	≥ 4.6		$p = 0.09$
MCV (m/s)	56.5 ± 5.0	54.2 ± 6.4	> 51.0	≤ 35.7		$p < 0.05$§
F-wave latency (ms)	28.1 ± 5.0	29.3 ± 3.9	< 27.7	≥ 33.2 (≥ 41.5‡)		$p = 0.09$
Distal CMAP duration (ms)	6.8 ± 1.3	6.6 ± 1.2	No data	≥ 6.7	≥ 9.6	$p = 0.58$
Tibial nerve						
CMAP amplitude (mV)	6.8 ± 6.0	4.1 ± 5.6	> 6.0			$p < 0.05$§

CMAP amplitude ≤ 1.0 mV (n)[I]	8	33				$p < 0.01$[¶]
DL (ms)	4.5 ± 0.9	5.4 ± 2.2	< 5.1	≥ 7.6		$p = 0.24$
MCV (m/s)	44.5 ± 4.3	38.9 ± 7.7	> 39.0	≤ 27.3		$p < 0.01$[§]
F-wave latency (ms)	48.7 ± 5.0	49.9 ± 8.1	< 51.6	≥ 61.9 (≥ 77.4[‡])		$p = 0.13$
Distal CMAP duration (ms)	5.9 ± 1.5	5.0 ± 1.7	No data	≥ 8.8	≥ 9.2	$p < 0.05$[§]

Each value is expressed as numbers of patients or mean ± SD.

[*] Cut-off value calculated from normal value based on the EFNS/PNS electrodiagnostic criteria.

[†] Upper value for distal CMAP duration in 2-Hz low-cut filter proposed by Mitsuma et al. [19]

[‡] Upper value if CMAP amplitude ≤ 20% of normal value.

[§] Statistically significant difference after Mann-Whitney U test.

[I] CMAPs disappeared in three and ten patients from endemic and non-endemic areas, respectively.

[¶] Statistically significant difference after Fisher's exact test.

CMAP, compound muscle action potential; DL, distal latency; EFNS/PNS, European Federation of Neurological Societies/Peripheral Nerve Society; MCV, motor conduction velocity.

Table 3 Number of patients with each demyelinating parameter that meet the EFNS/PNS EDX criteria

Electrophysiological parameters	Ulnar nerve (n/N)	Tibial nerve (n/N)
DL prolongation	1/102	9/89
MCV reduction	1/102	3/88
F-wave latency prolongation or absence	8/97	0/83
Distal CMAP duration prolongation	45/101	4/89
Distal CMAP duration prolongation (Mitsuma et al.*)	2/101	3/89
Abnormal temporal dispersion	2/101	9/88
Conduction block	0/102	0/89

The number of subjects with positive finding/total subjects who were able to measure or assess each parameter is indicated as n/N.

* Upper value for distal CMAP duration in 2-Hz low-cut filter proposed by Mitsuma et al. [19].

CMAP, compound muscle action potential; DL, distal latency; EDX: electrodiagnostic; EFNS/PNS, European Federation of Neurological Societies/Peripheral Nerve Society; MCV, motor conduction velocity.

Table 4 Demyelinating parameters in patients with definite EFNS/PNS EDX criteria

	Patient No.												
Electrophysiological parameters	1	2	3	4	5	6	7	8	9	10	11	12	13
Ulnar nerve													
CMAP amplitude, mV	8.50	8.92	8.90	2.22	2.35	4.70	3.38	1.01	4.59	2.90	4.88	2.25	0.23
DL prolongation													(+)
MCV reduction													(+)
F-wave latency prolongation or absence				(+)			(+)					(+)	
Distal CMAP duration prolongation	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
Distal CMAP duration prolongation (Mitsuma et al.*)								(+)					
Abnormal temporal dispersion								(+)					

Table 4 Demyelinating parameters in patients with definite EFNS/PNS EDX criteria (continued)

Electrophysiological parameters	Patient No.												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Tibial nerve													
CMAP amplitude, mV	1.20	1.86	1.25	0.58	0.01	1.13	1.75	0.03	0.11	0.05	0.63	0.01	0.17
DL prolongation					(+)			(+)	(+)	(+)		(+)	
MCV reduction										(+)			
F-wave latency prolongation or absence													
Distal CMAP duration prolongation						(+)			(+)				
Distal CMAP duration prolongation (Mitsuma et al.*)						(+)			(+)				
Abnormal temporal dispersion	(+)	(+)	(+)			(+)					(+)		

* Upper value for distal CMAP duration in 2-Hz low-cut filter proposed by Mitsuma et al. [19].

CMAP, compound muscle action potential; DL, distal latency; EDX: electrodiagnostic;

EFNS/PNS, European Federation of Neurological Societies/Peripheral Nerve Society; MCV, motor conduction velocity.

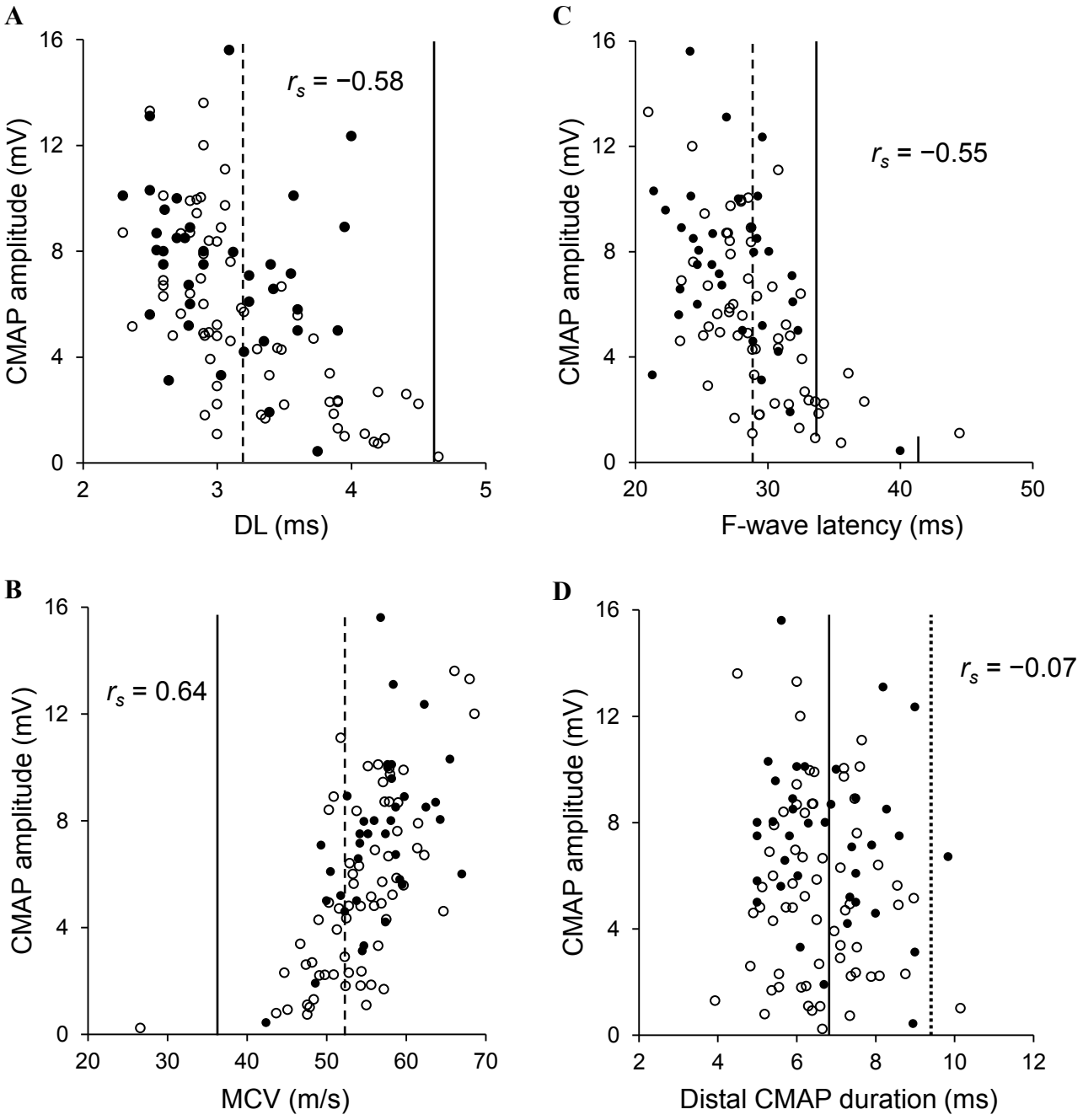
Table 5 Comparison between patients with and without definite EFNS/PNS EDX criteria

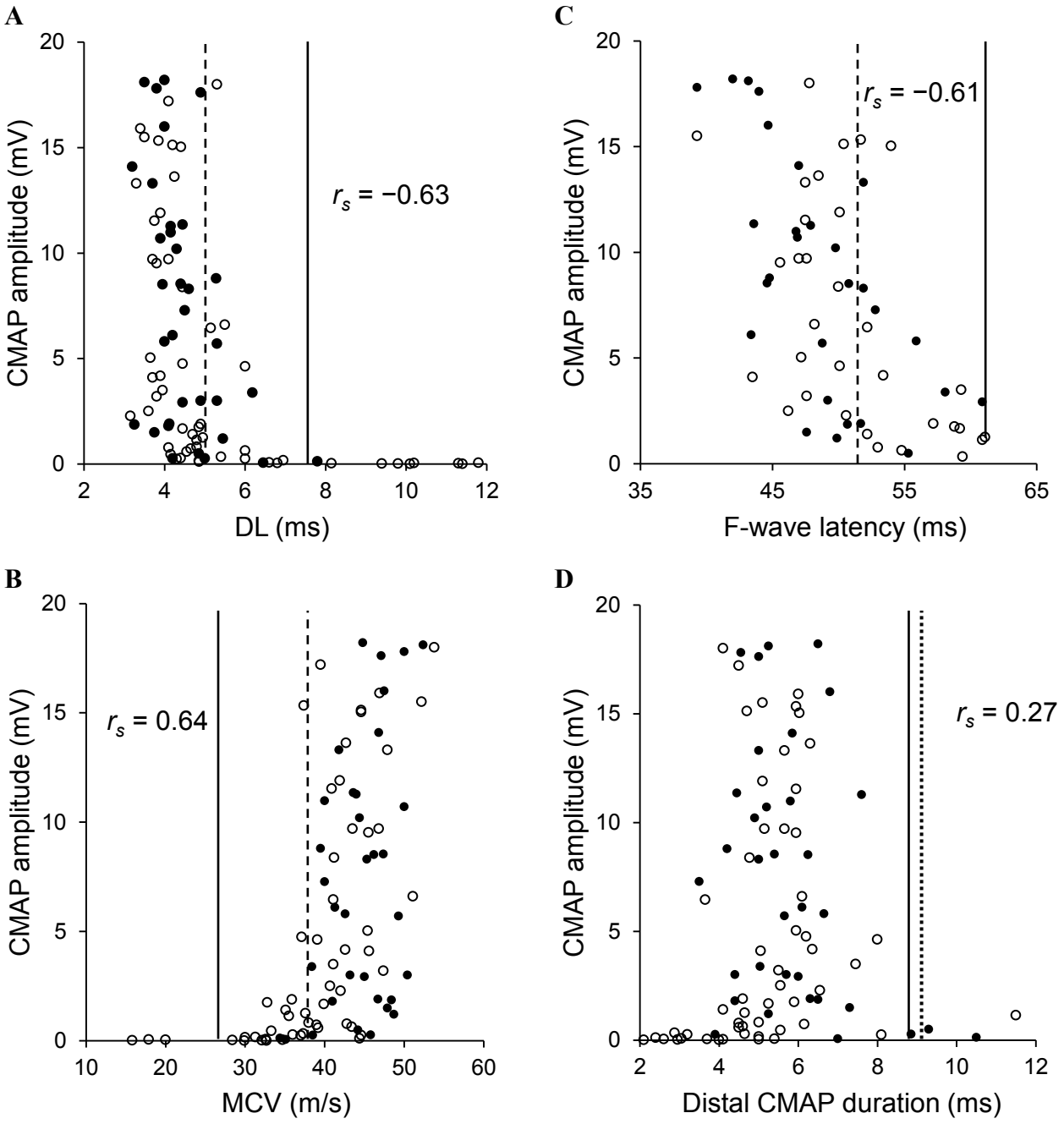
	Patients with EFNS/PNS EDX definite CIDP n = 13	Patients without EFNS/PNS EDX definite CIDP n = 89	*p* Value
Women/men	3/10	32/57	$p = 0.53$
Endemic areas/non-endemic areas	3/10	34/55	$p = 0.37$
TTR mutation			
Val30Met/non-Val30Met[*]	11/2	74/15	$p = 1.00$
Presence of family history	7	69	$p = 0.09$
Age of neurological onset (years)	54.3 ± 15.2	47.1 ± 17.2	$p = 0.20$
Duration from neurological onset to electrophysiological study (years)	4.2 ± 2.5	3.1 ± 2.3	$p = 0.12$
Clinical stage[†]			
Stage 0	0	7	$p = 0.59$
Stage I	9	72	$p = 0.46$
Stage II	3	9	$p = 0.17$
Stage III	1	1	$p = 0.24$

[*] 3 Ser50Arg (p.Ser70Arg), 2 Asp38Ala (p.Asp58Ala), 2 Phe44Ser (p.Phe64Ser), 2 Thr60Ala (p.Thr80Ala), 2 Gly42Arg (p.Gly62Arg), 1 Glu42Gly (p.Glu62Gly), 1 Arg54Thr (p.Arg74Thr), 1 Ile107Val (p.Ile127Val), 1 Ile84Asn (p.Ile104Asn), 1 Ser50Ile (p.Ser70Ile), 1 Tyr114His (p.Tyr134His).

[†] Clinical stages of hereditary ATTR amyloidosis as defined by Countinho et al. [30]. Stage 0: patients have some autonomic dysfunction but lack polyneuropathic symptoms or signs, stage I: polyneuropathy is localized to lower limbs, and patients can walk without help, stage II: polyneuropathy involves upper and lower limbs; patients are handicapped but can still walk with help, stage III: severe polyneuropathy and autonomic dysfunction confines patients to wheelchair, or they are bedridden.

CMAP, compound muscle action potential; DL, distal latency; EDX: electrodiagnostic; EFNS/PNS, European Federation of Neurological Societies/Peripheral Nerve Society; MCV, motor conduction velocity.


A
r_s = −0.58
CMAP amplitude (mV)
DL (ms)
C
r_s = −0.55
CMAP amplitude (mV)
F-wave latency (ms)
B
r_s = 0.64
CMAP amplitude (mV)
MCV (m/s)
D
r_s = −0.07
CMAP amplitude (mV)
Distal CMAP duration (ms)


A
CMAP amplitude (mV)
DL (ms)
r_s = −0.63
C
CMAP amplitude (mV)
F-wave latency (ms)
r_s = −0.61
B
CMAP amplitude (mV)
MCV (m/s)
r_s = 0.64
D
CMAP amplitude (mV)
Distal CMAP duration (ms)
r_s = 0.27