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Length-dependent truncal Aδ-fiber dysfunction in hereditary transthyretin amyloidosis: An intra-epidermal electrical stimulation study

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HIGHLIGHTS

- Intra-epidermal electrical stimulation (IES) can selectively activate Aδ-fibers in the skin.
- Length-dependent truncal Aδ-fiber dysfunction in ATTRm amyloidosis was demonstrated using IES.
- IES may be clinically useful for investigating Aδ-fiber dysfunction at various parts of the body.

ABSTRACT

Objective: To elucidate Aδ-fiber dysfunction at the trunk in patients with hereditary transthyretin (ATTRm) amyloidosis using intra-epidermal electrical stimulation (IES).
Methods: In 16 patients with ATTRm amyloidosis and 18 healthy subjects, sensory thresholds using IES and cooling detection thresholds using the Computer-Aided Sensory Evaluation (CASE IV) system, were assessed to investigate Aδ-fiber functions at the Th10 level of the anterior, lateral, and posterior trunk. Furthermore, evoked potentials (EPs) following electrical stimulation using IES at the anterior and posterior trunk were evaluated.
Results: In patients with ATTRm amyloidosis, both IES and CASE IV sensory thresholds tended to be higher at the anterior trunk than at the lateral and posterior trunks. The amplitudes of EPs following electrical stimulation at the anterior trunk were lower than those at the posterior trunk. Aδ-fiber dysfunction at the anterior trunk was conspicuous in patients with more intense polyneuropathy at the limbs. In healthy subjects, there were no differences in both sensory thresholds and EP amplitudes among any examination sites. Sensory thresholds with IES and CASE IV were correlated.
Conclusions: Evaluation using IES demonstrated length-dependent Aδ-fiber dysfunction at the trunk in patients with ATTRm amyloidosis.
Significance: IES may be a useful clinical tool for investigating Aδ-fiber dysfunction at various parts of the body in patients with neuropathy.
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1. Introduction

Hereditary transthyretin (ATTRm) amyloidosis, also known as transthyretin familial amyloid polyneuropathy (ATTR-FAP), is an autosomal dominant inherited disorder (for review, see Planté-Bordeneuve and Said, 2011). After transthyretin (TTR) deposition, most patients with ATTRm amyloidosis develop sensory and motor axonal neuropathy with or without various forms of organ dysfunction in the heart, kidney, eyes, and autonomic nervous system.

Abbreviations: ATTR-FAP, transthyretin familial amyloid polyneuropathy; ATTRm amyloidosis, hereditary transthyretin amyloidosis; CASE IV, Computer-Aided Sensory Evaluation; EP, evoked potential; IES, intra-epidermal electrical stimulation; IENFD, intra-epidermal nerve fiber density; QST, quantitative sensory testing; TTR, transthyretin.

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The neuropathy in ATTRm amyloidosis shows a characteristic distribution and sensory deficit pattern (Andrade, 1952). Patients with ATTRm amyloidosis show polyneuropathy with a length-dependent pattern in the limbs; the neuropathic symptoms and signs start at the most distal part of the lower legs and progress to the proximal region, after which the distal part of the upper limbs is involved. Predominant dysfunction of small fibers (Aδ- and C-fibers that are related to pain and temperature sensations), known as dissociated sensory disturbances, is another typical clinical feature, especially in ATTRm amyloidosis patients harboring the V30M mutation from an endemic area (Koike et al., 2002). Clinically, sensory loss at the anterior trunk is also recognized in patients with ATTRm amyloidosis (Said et al., 1984; Ikeda et al., 1987). This truncal sensory sign is considered to be caused by a length-dependent polyneuropathy of the intercostal nerves. However, truncal polyneuropathy in patients with ATTRm amyloidosis has not been investigated systematically. One reason for this is that conventional nerve conduction studies, the most common neurophysiological tool for evaluating neuropathy, can usually assess only large-fiber (Aα and Aβ fibers) function in the limbs (Kodaira et al., 2011).

Intra-epidermal electrical stimulation (IES) has been recently developed as a new technique for activating Aδ-fibers in the superficial layer of the skin (for review, see Inui and Kakigi, 2012). Basic studies have demonstrated that IES using low electrical intensity stimulation can stimulate Aδ-fibers selectively by comparing the results to those obtained with laser stimulation (Inui et al., 2002; Mouraux et al., 2010). Two studies using an experimental model of small-fiber neuropathy with transdermal lidocaine showed that IES can detect Aδ-fiber dysfunction via evaluation of the sensory threshold and evoked potentials (EPs) (Otsuru et al., 2010; Kodaira et al., 2014). Two clinical studies using IES for assessing sensory thresholds demonstrated its clinical usefulness for detecting Aδ-fiber dysfunction at the foot in a patient with amyloid neuropathy (Obayashi et al., 2011) and patients with diabetic neuropathy (Suzuki et al., 2016). However, there are no clinical studies comparing the results of IES with those of other well-established methods for evaluating small-fiber function, such as laser-evoked potentials, quantitative sensory testing (QST), and intra-epidermal nerve fiber density (IENFD). A basic study in healthy subjects showed the potential of IES in activating Aδ-fibers at various parts of the body, including the trunk (Omori et al., 2013); however, there are no clinical studies using IES for investigating Aδ-fiber dysfunction at any sites except the limbs. This study aimed to evaluate Aδ-fiber dysfunction at the trunk in patients with ATTRm amyloidosis using IES and compare the results with those obtained by cooling detection threshold analysis using the Computer-Aided Sensory Evaluation (CASE IV) system (Dyck et al., 1993a), a QST method.

2. Methods

2.1. Subjects

Patients with ATTRm amyloidosis (n = 16) and healthy subjects (n = 18) were included in this study. Considering the influence of age on the results for sensory thresholds and EPs, participants over 50 years of age were excluded from this study. Patients with other causes of neuropathy such as diabetes mellitus were also excluded. In patients with ATTRm amyloidosis, the diagnosis was confirmed by evaluation of TTR-derived amyloid deposition in biopsy specimens and the identification of disease-causing mutations in the *TTR* gene. All patients showed symptoms and/or signs associated with polyneuropathy in the limbs, except two patients who did not show any clinical symptoms and signs of ATTRm amyloidosis. Clinically, 13 of the 14 patients with polyneuropathy exhibited sensory symptoms and signs with small-fiber predominance. Thirteen and four patients, respectively, showed dysesthesia and neuropathic pain, especially in the lower limbs. On the other hand, only two patients complained of decreased pain and temperature perception at the anterior trunk before this study; both of them experienced severely reduced pain and cold sensation for wound and disinfectant at the anterior trunk just after liver transplantation. None of the patients experienced any positive sensory symptoms such as pain and dysesthesia at the trunk. One patient was a man with iatrogenic ATTRm amyloidosis; the patient with adult-onset type II citrullinemia was a domino recipient who underwent domino liver transplantation from an ATTRm amyloidosis patient harboring a V30L mutation. He developed typical neuropathic symptoms compatible with ATTRm amyloidosis 10 years after the domino liver transplantation. Fifteen of the 16 patients with ATTRm amyloidosis were treated with liver transplantation and/

Table 1
Clinical background.

Features	ATTRm amyloidosis patients (n = 16)	Healthy subjects (n = 18)	Differences[a]
Women/men	7/9	5/13	$p = 0.48$
Age at examinations (years)	39 [34–45]	33 [31–36]	$p = 0.05$
Height (cm)	165 [160–173]	165 [162–167]	$p = 0.83$
Truncal circumference around the Th10 level (cm)	80 [74–89]	85 [77–88]	$p = 0.30$
TTR mutation			
V30M/non-V30M[b]	9/7		
Duration of neuropathy (years)	5.8 [4.0–9.0]		
Duration from neurological onset to therapy[c] (years)	2.0 [1.3–4.0]		
Neuropathic symptoms and signs			
Polyneuropathy in the limbs	14		
Orthostatic hypotension	12		
Vomiting/diarrhea/constipation	11		
Impotence	4		
Dysuria	4		
Clinical stage[d]			
Stage 0/I/II/III	2/5/9/0		

Each value is expressed as numbers of patients or median [interquartile range].
ATTRm amyloidosis, hereditary transthyretin amyloidosis; TTR, transthyretin.
[a] Analyzed using Fisher's exact test or Mann-Whitney U test.
[b] Non-V30M include: 2 S50A, 2 P44S, 2 G42A, 1 V30L.
[c] Therapy includes liver transplantation or TTR stabilizers.
[d] Clinical stage of ATTRm amyloidosis is described in the method.

or TTR stabilizers. None of the healthy subjects showed neurological abnormalities. The background information of the patients and healthy subjects is summarized in Table 1. This study was approved by the Committee for Medical Ethics of Shinshu University School of Medicine. Written informed consent was obtained from each subject.

2.2. Study design

Subjects visited the examination room twice for sensory threshold assessment and EP recording sessions. Sensory threshold assessment was performed at the first visit, and EPs were recorded at the second visit. The two visits were separated by a 2-week interval. For assessment of sensory threshold-related Aδ-fiber function, sensory thresholds were investigated using both CASE IV and IES. We assessed the cooling detection threshold with CASE IV at the Th10 level of the anterior, lateral, and posterior trunk. Subsequently, the sensory threshold with IES was evaluated at the same sites. The two sensory threshold assessments at the same sites were separated by an interval of more than 15 min. EPs were recorded using IES at the Th10 level of the anterior and posterior trunk.

2.3. Procedure

The subjects were laid in a bed in a quiet examination room. Examinations of the anterior, lateral, and posterior trunk were performed in the supine, lateral, and prone positions, respectively. Examination of each session was started at the anterior trunk, followed by testing at the lateral and posterior trunk. The Th10 level of the anterior and posterior trunk was set using the spinous process and umbilicus as hallmarks, respectively. The examination sites on the anterior and posterior trunk were defined as approximately 2–3 cm left lateral of the umbilicus and spinous process, respectively. The lateral trunk was defined as the mid-site between the anterior and posterior trunk. Skin temperatures above 31 °C at the examination sites were confirmed at the beginning of each investigation.

2.4. Cooling detection threshold assessment

The cooling detection threshold with CASE IV (WR Medical Electronics Co., Minnesota, United States) was assessed as described in previous studies (Dyck et al., 1993a; Zinman et al., 2004). Using the examiner's hand, the stimulator with a 30 × 30-mm thermoelectric element contacting the skin was attached gently at each examination site. At the beginning of each examination, the skin temperature was automatically set to a baseline temperature of 30 °C. Then, cooling stimulation controlled by the computer was presented using the 4-2-1 testing algorithm in a staircase procedure (Dyck et al., 1993b). After 20 cooling stimulations with some randomized null stimuli, the cooling detection threshold was determined as 30–X °C. We defined the threshold as X °C hereafter. The maximum cooling detection threshold obtained using CASE IV was 21 °C. A threshold of 21 °C was assigned if the subjects did not experience any sensation under the maximum cooling level.

2.5. Sensory threshold assessment with IES

The sensory threshold related to selective Aδ-fiber activation was assessed using IES as described previously (Kodaira et al., 2014). For selective Aδ fiber stimulation, a stimulating electrode with three concentric bipolar needle electrodes that were 6 mm apart (NM-983W; Nihon Kohden, Tokyo, Japan) and a portable peripheral nerve stimulator (PNS-7000; Nihon Kohden) were used. Each concentric bipolar needle electrode consisted of an outer ring with a diameter of 1.3 mm and an inner needle protruding 0.02 mm from the outer ring. The inner needle and outer ring of each electrode were used as the cathode and anode, respectively. The electric pulse was a triangular wave with a rise and fall time of 0.5 ms. A train of double pulses with an interstimulus interval of 10 ms was used. To determine the sensory threshold with IES, we used a staircase procedure. We started stimulation with an intensity of 16.7 μA in each electrode. The intensity of the current was increased in steps of 6.7 μA until the subjects felt a weak sensation such as pricking and tingling. Then, we decreased the intensity in steps of 3.3 μA until the sensation disappeared. PNS-7000 can present a maximum electrical intensity of 333 μA. A threshold of 333 μA was assigned if the subjects could not detect any sensation under the maximum stimulus intensity. For each examination site of the trunk, the sensory threshold with IES was assessed at four different locations, from which we calculated the mean threshold value. The mean value was defined as the sensory threshold at each site.

2.6. EP recording and stimulus detection rate

We recorded EPs using IES as previously reported (Kodaira et al., 2014). Using electroencephalography (EEG), EPs with negative (N2) and positive (P2) components were recorded as vertex potentials. The Cz electrode and linked earlobes (A1A2) were used as the active and reference electrodes, respectively. The impedance of the electrodes was kept below 5 kΩ. For selective Aδ-fiber stimulation at both the anterior and posterior trunk, the intensity of the stimulus was fixed at 1.6 times the sensory threshold of each subject at the posterior trunk in the threshold assessment session. The stimulus was presented with an interstimulus interval of 10–15 s. The EEG signals were recorded 200 ms before to 800 ms after the onset of stimulation with a band-pass filter of 0.1–100 Hz at a sampling rate of 2000 Hz. The 200-ms period before the stimulation was used as the DC baseline. For each site, at least 12 (median, 15; range, 12–20) artifact-free EEG signals were recorded and averaged. The N2 peak was defined as the negative deflection between 120 and 420 ms. The P2 peak was defined as the positive deflection between 230 and 600 ms. During the first 15 electrical stimuli for EP recordings at each site, subjects were instructed to count the number of stimuli detected.

2.7. Statistical analysis

In the ATTRm amyloidosis and healthy subject groups, differences in sensory thresholds, parameters of EPs, and stimulus detection rates among examination sites were analyzed using the Wilcoxon signed-rank test or Friedman test. If the differences among the three sites were significant, Scheffe's multiple comparison analysis was performed. Correlations between sensory thresholds with CASE IV and IES in all subjects and sites were analyzed using Spearman's rank correlation coefficient. The correlation between each sensory threshold and the amplitude of EPs in all subjects and sites was also analyzed using Spearman's rank correlation coefficient. To analyze the relationship between length-dependent neuropathy at the limbs and the trunk in patients with ATTRm amyloidosis, we used a slightly modified version of the clinical stage defined by Coutinho et al. (1980). This modified clinical stage roughly reflects the degree of length-dependent polyneuropathy in the limbs as follows: stage 0, lack of polyneuropathic symptoms or signs; stage I, polyneuropathy is localized to the lower limbs; stage II, polyneuropathy involves the upper and lower limbs, but the patients can still walk; stage III, severe polyneuropathy and autonomic dysfunction that confines patients to a wheelchair or renders them bedridden. We compared sensory thresholds, parameters of EPs, and stimulus detection rates at the

anterior trunk between ATTRm amyloidosis patients with stage 0 + I (n = 7) and those with stage II (n = 9) using the Mann-Whitney *U* test. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using Bell Curve for Excel (Social Survey Research Information Co., Ltd, Tokyo, Japan).

3. Results

3.1. Sensory thresholds

Figs. 1 and 2 show the sensory thresholds as measured using CASE IV and IES, respectively. The median and interquartile range (IQR) of both sensory thresholds are summarized in Table 2. In patients with ATTRm amyloidosis, there were significant differences in both sensory thresholds with CASE IV ($p < 0.001$) and IES ($p < 0.005$) among the examination sites. In comparison with the cooling detection threshold at the anterior trunk, the threshold tended to be low ($p = 0.05$) and was lower ($p < 0.001$) at the posterior and lateral trunk, respectively. The sensory threshold with IES was higher at the anterior trunk than that at the posterior trunk ($p = 0.004$). The threshold appeared to be higher at the anterior trunk than that at the lateral trunk, but the difference was not statistically significant ($p = 0.15$). There were no significant differences in sensory thresholds between the lateral and posterior trunk with either CASE IV ($p = 0.40$) or IES ($p = 0.37$). In healthy

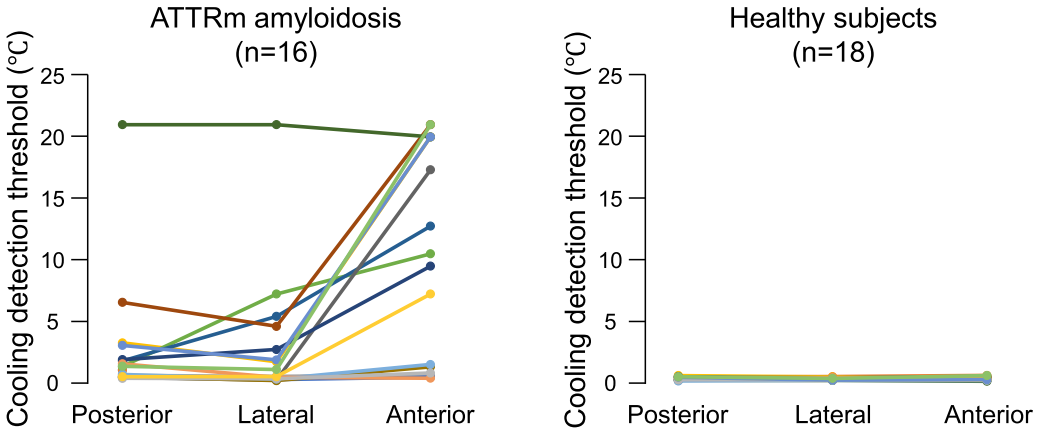

Fig. 1. Cooling detection threshold with CASE IV. Cooling detection threshold was elevated at the anterior trunk compared to those at the lateral and posterior trunk in patients with ATTRm amyloidosis. There were no differences in the cooling detection thresholds among three sites in healthy subjects.

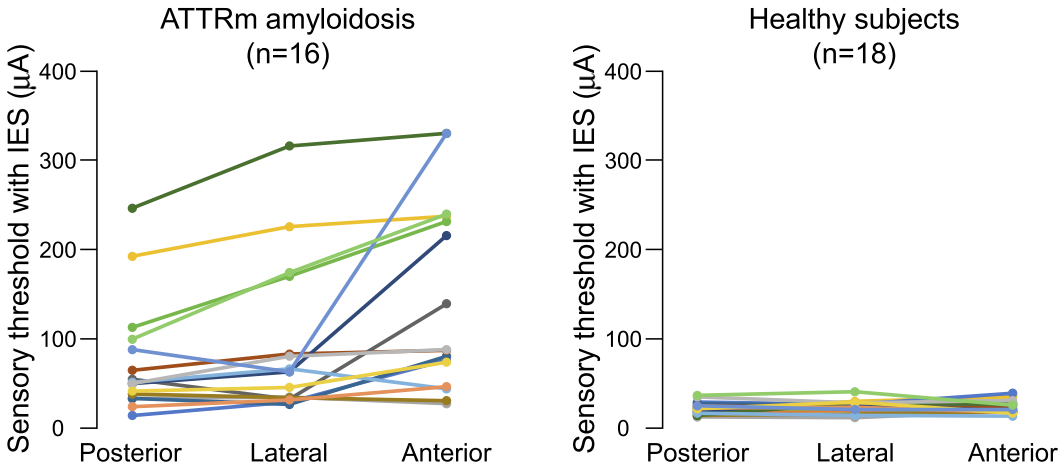

Fig. 2. Sensory threshold with IES. Sensory threshold with IES was elevated at the anterior trunk compared to that at the posterior trunk in patients with ATTRm amyloidosis. Sensory threshold at the anterior trunk tended to be higher than that at the lateral trunk. There were no differences in sensory threshold among the three sites in healthy subjects.

Table 2
Sensory thresholds.

	Posterior trunk	Lateral trunk	Anterior trunk
Cooling detection threshold (°C)			
ATTRm amyloidosis patients	1.29 [0.44–2.13]	0.76 [0.27–3.14]	9.97 [1.13–20.0]
Healthy subjects	0.36 [0.17–0.40]	0.17 [0.16–0.28]	0.17 [0.17–0.33]
Sensory threshold with IES (μA)			
ATTRm amyloidosis patients	52.5 [38.8–92.9]	65.0 [35.4–106.9]	89.6 [69.0–235.6]
Healthy subjects	21.7 [17.7–25.0]	23.8 [21.0–27.9]	21.3 [18.5–27.9]

Each value is expressed as median [interquartile range].
ATTRm amyloidosis, hereditary transthyretin amyloidosis; IES, intra-epidermal electrical stimulation.

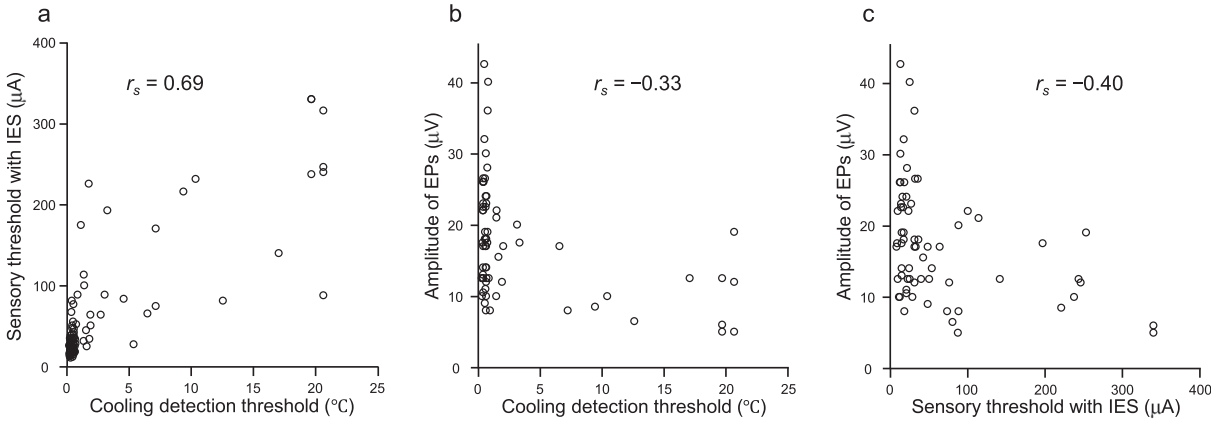

Fig. 3. Correlation between sensory thresholds with CASE IV and IES, and amplitude of EPs. The sensory thresholds measured by CASE IV and IES were positively correlated (a). The amplitude of EPs was negatively correlated with sensory thresholds measured by both CASE IV (b) and IES (c).

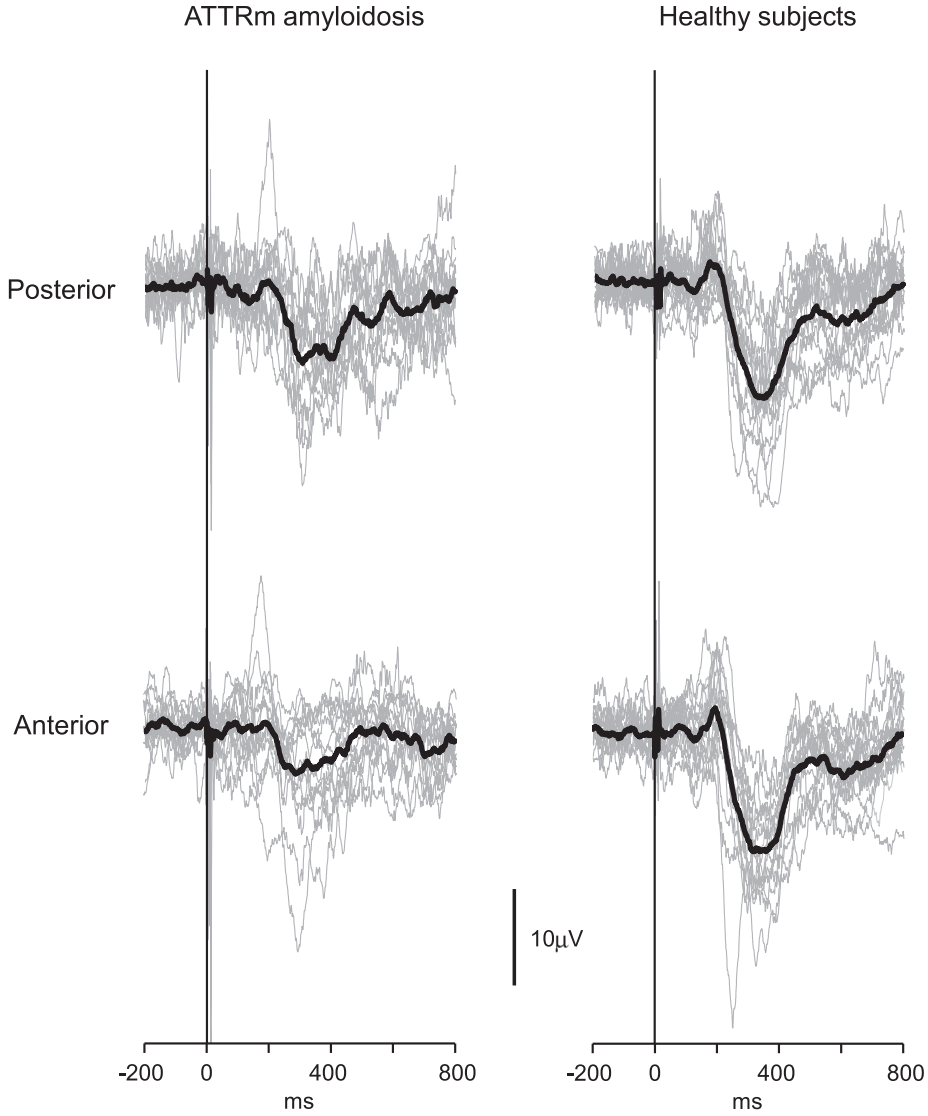

Fig. 4. EPs. Thick black and thin gray lines show the grand-averaged waveforms and the superimposed waveforms of EPs of all subjects, respectively. In patients with ATTRm amyloidosis, the amplitude of EPs decreased at the anterior trunk compared to that at the posterior trunk. In healthy subjects, there was no difference in the amplitude of EPs between the two examination sites.

Table 3
EPs.

	Posterior trunk	Anterior trunk
N2P2 amplitude (μV)		
ATTRm amyloidosis patients	17.0 [12.5–19.5]	10.0 [7.3–12.3]
Healthy subjects	17.8 [13.6–23.8]	20.8 [14.9–26.0]
N2 latency (ms)		
ATTRm amyloidosis patients	192 [163–202]	220 [192–251]
Healthy subjects	185 [172–202]	202 [196–213]
P2 latency (ms)		
ATTRm amyloidosis patients	338 [313–388]	360 [303–450]
Healthy subjects	332 [319–350]	363 [325–384]

Each value is expressed as median [interquartile range].
ATTRm amyloidosis, hereditary transthyretin amyloidosis; EPs, evoked potentials.

subjects, there were no significant differences in both sensory thresholds with both CASE IV and IES among the examination sites ($p = 0.18$ and $p = 0.79$, respectively). As shown in Fig. 3a, there was a significant positive correlation between both sensory thresholds ($r_s = 0.69$, $p < 0.001$). The length-dependent elevating pattern of the sensory threshold with CASE IV and/or IES (anterior > lateral > posterior trunk) was apparent in patients with ATTRm amyloidosis (n = 11/16) compared to healthy subjects (n = 5/18) ($p = 0.04$, Fisher's exact test). Cooling stimulation induced no pain sensation in patients with ATTRm amyloidosis or the healthy subjects.

3.2. EPs

The waveforms of EPs are demonstrated in Fig. 4. The amplitude and latency of the EPs are summarized in Table 3. One of the ATTRm amyloidosis patients with clinical stage I disease was excluded from the analysis of EPs because of missing data due to an EEG recording machine problem. In patients with ATTRm amyloidosis, the amplitudes of EPs following stimulation at the anterior trunk were lower than those after stimulation at the posterior trunk ($p = 0.006$). There were no differences in the amplitude of EPs between both examination sites in healthy subjects ($p = 0.32$). The EP amplitudes were negatively correlated with sensory thresholds measured using CASE IV ($r_s < -0.33$, $p = 0.007$, Fig. 3b) and IES ($r_s = -0.40$, $p < 0.001$, Fig. 3c).

The N2 latency of EPs following stimulation at the anterior trunk was longer than those following stimulation at the posterior trunk in patients with ATTRm amyloidosis ($p = 0.01$) and healthy subjects ($p = 0.01$). The P2 latency of EPs following stimulation at the anterior trunk tended to be longer than those following stimulation at the posterior trunk in healthy subjects ($p = 0.12$). However, there was no significant difference in the P2 latency in patients with ATTRm amyloidosis ($p = 0.21$). This may be caused by fluctuation of the P2 latency following decreased EP amplitude due to severe Aδ-fiber dysfunction in patients with ATTRm amyloidosis.

3.3. Stimulus detection rate

In patients with ATTRm amyloidosis, the number of stimuli detected following 15 electrical stimulations was lower at the anterior trunk (median, 8.5; IQR, 1–14) compared to that at the posterior trunk (median, 14.5; IQR, 12–15; $p = 0.01$). In healthy subjects, there were no significant differences in the number of stimuli detected between the anterior trunk (median, 15; IQR, 14–15) and the posterior trunk (median, 15; IQR, 13.3–15; $p = 0.26$).

3.4. Relationship between Aδ-fiber dysfunction at the anterior trunk and clinical stage

Table 4 summarizes the relationship between the results for each parameter at the anterior trunk and the clinical stage in patients with ATTRm amyloidosis. Sensory thresholds with CASE IV and IES at the anterior trunk were higher in patients with stage II disease than in those with stage 0 + I disease. On the other hand, the amplitude of EPs did not differ between the two groups. This may be attributable to the stronger electrical stimulation due to the higher sensory threshold with IES at the posterior trunk in patients with stage II disease (median, 90.0 μA; IQR, 53.3–115.0 μA) than in those with stage 0 + I disease (median, 40.0 μA; IQR, 30.4–47.5 μA; $p = 0.009$). In each subject, we set the intensity of electrical stimulation for recording EPs at 1.6 times the sensory threshold at the posterior trunk. During EP recording, a stronger stimulation intensity in patients with stage II disease may activate more Aδ fibers. Indeed, the number of stimuli detected at the anterior trunk did not differ between patients with stage 0 + I and stage II disease. In an analysis of the ratios of EP amplitude at the anterior trunk/EP amplitude at the posterior trunk, the ratio was lower in patients with stage II disease (median, 0.50; IQR, 0.32–0.55) than in those with stage 0 + I disease (median, 0.89; IQR, 0.70–1.06; $p = 0.03$). There were no differences in degree of Aδ-fiber dysfunctions at the anterior trunk between patients with V30M and non-V30M mutations (Mann-Whitney *U* test, data not shown).

4. Discussion

This study using IES demonstrated length-dependent Aδ fiber dysfunction at the trunk in patients with ATTRm amyloidosis. In patients with ATTRm amyloidosis, sensory thresholds measured using CASE IV and IES tended be higher at the anterior trunk than at other sites. The EP amplitudes at the anterior trunk were lower than those at the posterior trunk. Aδ-fiber dysfunction at the anterior trunk was stronger in patients with more intense polyneuropathy in the limbs. On the other hand, sensory thresholds and EP amplitudes did not change at any sites of the trunk in healthy subjects. The sensory thresholds with CASE IV and IES were strongly correlated. These results support the notion that IES is a useful clinical tool for evaluating Aδ-fiber dysfunction at various parts of the body.

4.1. Evaluation of Aδ-fiber dysfunction using IES

For evaluating Aδ- and C-fiber functions in patients with small-fiber neuropathy, various neurophysiological (laser- and contact

Table 4
Relationship between Aδ-fiber dysfunction at the anterior trunk and clinical stage.

Parameters	Stage 0 + I (n = 7)	Stage II (n = 9)	Differences
Cooling detection threshold (°C)	0.75 [0.50–4.22]	20.00 [10.47–20.00]	$p = 0.003$
Sensory threshold with IES (μA)	75.8 [40.4–84.2]	234.2 [89.2–242.5]	$p = 0.02$
EP amplitude (μV)	11.0 [8.5–12.4]	8.5 [6.0–12.0]	$p = 0.28$
Number of stimuli detected	8 [5.5–14]	9 [0–12]	$p = 0.55$

Each value is expressed as median [interquartile range].
EPs, evoked potentials; IES, intra-epidermal electrical stimulation.

heat-evoked potentials), psychophysiological (QST), and neuropathological (IENFD) approaches have been used (for review, see Hoitsma et al., 2004). IES has been developed as a new technique for activating Aδ-fibers in the superficial layer of the skin (Inui and Kakigi, 2012). If the use of an intense stimulus intensity (e.g., 2.5 mV) is avoided, which co-activates Aβ-fibers located in the deeper layer of the skin, IES can activated Aδ-fibers selectively (Mouraux et al., 2010). The advantages of IES include its convenience and non-invasiveness in comparison with other methods. However, only a few studies have demonstrated the clinical utility of IES for investigating small-fiber dysfunction in patients with neuropathy (Obayashi et al., 2011; Suzuki et al., 2016).

In this study, the results of sensory threshold with IES were well correlated with those of cooling detection thresholds determined by using CASE IV. Intense cold stimulation was given to some of the ATTRm amyloidosis patients with severely reduced temperature sensation, but they did not complain of any pain sensation. Innocuous cold sensation is mainly mediated by Aδ fibers (Mackenzie et al., 1975; Schepers and Ringkamp, 2010). The results for the sensory thresholds suggested that IES detects Aδ-fiber dysfunction in patients with ATTRm amyloidosis.

As for EPs, the amplitude decreased with elevation of sensory threshold, similar to previous studies using an experimental model of small-fiber neuropathy with transdermal lidocaine (Otsuru et al., 2010; Kodaira et al., 2014). A study using laser-evoked potentials showed that the mean P2 latency following laser stimulation at the Th12 vertebral spinous processes was 362.6 ms (Qiu et al., 2001). Around a 40-ms latency difference in EPs was known between electrical and laser stimulations due to the temperature conduction time in the skin for the latter (Inui et al., 2002). Considering the latency of EPs at the posterior trunk (median, 338 and 332 ms in patients with ATTRm amyloidosis and healthy subjects, respectively), the findings also supported selective Aδ-fiber stimulation using IES in our study. Furthermore, this was the first clinical study to use IES to evaluate Aδ-fiber dysfunction at a site other than the limbs. The results of our study suggest that IES has the potential to serve as a clinical tool for investigating small-fiber dysfunction at various parts of the body in patients with neuropathy.

4.2. Length-dependent truncal polyneuropathy in ATTRm amyloidosis

In addition to global and stoking neuropathic symptoms in the limbs, sensory deficits at the anterior trunk have been clinically recognized in patients with ATTRm amyloidosis (Said et al., 1984; Ikeda et al., 1987). The pathophysiology of this length-dependent polyneuropathy is presumed to be attributable not only to direct compression of nerve fibers by amyloid but also to the toxic effects of amyloid (Said et al., 1984; Hou et al., 2005). However, truncal polyneuropathy in patients with ATTRm amyloidosis has not been investigated systematically due to some reasons. Truncal polyneuropathy is presumed to occur in the advanced stage following progression of polyneuropathy in the limbs (Planté-Bordeneuve and Said, 2011). Furthermore, most of the patients with ATTRm amyloidosis do not show any positive sensory symptoms such as pain at the trunk even in later stage, although pain at the feet can be the initial and chief complaint (Andrade, 1952; Ikeda et al., 1987). Indeed, only two of 16 patients complained of decreased pain and cold sensations, and none of them showed positive symptoms at the trunk in our study. The reasons why few or no patients with ATTRm amyloidosis complain of sensory symptoms at the trunk, especially in neuropathic pain, are unclear. Ng Wing Tin et al. (2015) speculated that peripheral and central sensitization might induce neuropathic pain of the limbs in patients with early and advanced-stage ATTRm amyloidosis, respectively. However, this hypothesis alone cannot explain the truncal discrepancies because 11 of the 16 patients with ATTRm amyloidosis showed length-dependent elevation patterns of sensory thresholds with CASE IV and/or IES at the trunk in our study. Neuropathic pain at the lower limbs might induce diffuse noxious inhibitory control-like effect on the trunk (Pud et al., 2009).

To our knowledge, length-dependent truncal polyneuropathy has been scarcely reported in patients with other neuropathies except for those with advanced diabetic polyneuropathy (Waxman and Sabin, 1981; Said et al., 1983) and ATTRm amyloidosis. Using neurological examinations, Said et al. (2008) demonstrated that all of their 30 patients with severe length-dependent diabetic polyneuropathy in the four limbs had length-dependent truncal polyneuropathy. Patients with ATTRm amyloidosis from non-endemic areas sometimes show non-specific polyneuropathy without a family history and are occasionally misdiagnosed as those with other neuropathies such as chronic inflammatory demyelinating polyneuropathy (Planté-Bordeneuve et al., 2007; Koike et al., 2011). Planté-Bordeneuve et al. (2007) detected sensory loss not only at the four limbs but also at the anterior trunk in 68 of 90 sporadic patients with ATTRm amyloidosis by detailed neurological examination, although they did not report whether these patients experienced sensory loss at the trunk before the examination. Objective assessment of sensory dysfunction at the trunk might be useful for differential diagnosis in patients with suspected ATTRm amyloidosis, although assessments of these findings in patients with other neuropathies are needed.

4.3. Limitations

Our study has several limitations, including the small sample size and the unilateral investigation at a single dermatome level of Th10. This study was performed using neurophysiological and psychophysical tools, but the results were not confirmed by pathological assessment such as IENFD. The present study did not compare Aδ-fiber dysfunction at the trunk with that at the limbs directly. Furthermore, many patients with ATTRm amyloidosis had a long history of neuropathy and received therapy including liver transplantation and/or TTR stabilizers. Thus, we did not assess the natural history of this truncal polyneuropathy. Further investigations including pathological assessment are needed to elucidate the length-dependent truncal polyneuropathy in patients with ATTRm amyloidosis. As for clinical feasibility of IES, the fact that participants aged over 50 years were excluded from our study is a limitation as most patients with neuropathies, including those with ATTRm amyloidosis from non-endemic area, are older than 50 years (Koike et al., 2002). Studies in aged subjects are also needed for validation of the clinical utility of IES.

5. Conclusions

This study used IES to demonstrate length-dependent truncal Aδ-fiber dysfunction in patients with ATTRm amyloidosis. Although patients with ATTRm amyloidosis seldom complain of truncal sensory symptoms, decreased pain and temperature sensations at the anterior trunk may be a common clinical sign in these patients. IES may be a useful clinical tool for investigating Aδ-fiber dysfunction at various parts of the body in patients with neuropathy.

Author contributions

M.K. contributed to conception and design, acquisition of data, analysis, and interpretation of data, and drafting of the article. N.O. contributed to acquisition of data and revising the article. H.M. contributed to analysis and interpretation of data and revising

the article. Y.S. contributed to interpretation of data and revising the article.

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Declaration of interest

None.

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