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Progressive length-dependent polyneuropathy in xeroderma pigmentosum group A.

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We confirm that we have read the Journal's position on issues involved in ethical

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None of the authors has any conflict of interest to disclose.

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Abstract

Introduction: In this study, we aimed to investigate the progression of peripheral nervous system involvement in Xeroderma pigmentosum group A (XP-A) **Methods:** We performed nerve conduction studies in 17 genetically confirmed XP-A patients and conducted follow-ups. Of these patients we also analyzed gray matter volume (GMV) using brain MRI and assessed the severity score of clinical and skin manifestation. **Results:** We found significant reduction in the motor and sensory nerve action potential amplitude and mild reduction in conduction velocity. These findings were predominant in sensory nerves and the lower limbs, were observed since early childhood, and gradually deteriorated with age. **Discussion:** The electrophysiological characteristics of XP-A patients are consistent with length-dependent axonal polyneuropathy and there is progressive deterioration from early childhood.

Keywords: xeroderma pigmentosum, peripheral nervous system, nerve conduction study, length-dependent polyneuropathy, progressive deterioration,

early childhood

Introduction

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder characterized by hypersensitivity to sun exposure.[1)] There are seven XP complementation groups (XP-A through XP-G) and an XP variant (XP-V).[2)3)] The proteins encoded by *XPA* through *XPG* are involved in the DNA repair process known as nucleotide excision repair (NER), which repairs the damage caused by ultraviolet (UV) radiation.[2)4)] In approximately 60% of XP patients the initial symptom is severe sunburn reaction.[2)5)] Subsequently, various cutaneous symptoms occur and, without protection from sunlight, the risk of skin cancers remarkably increases from 2,000 to 10,000-fold. [2)5)]

Progressive neurodegeneration occurs in patients with XP-A, XP-B, XP-D, XP-F, and XP-G. The severity is different among the complementation groups and XP-A patients manifest the most severe symptoms[3)]. Various neurological symptoms including areflexia, loss of pain sensation, sensory ataxia,

microcephaly, intellectual disability, choreoathetosis, cerebellar ataxia, spasticity, and sensorineural deafness are recognized, resulting in death around the age of 30 years due to complications.[2)5)-13)] Thus, neurodegeneration and skin cancer are the major cause of death.[2)5)-11)] Although the risk of skin cancer can be reduced in XP patients by rigorous protection from the sun, there is no effective treatment to alter the progression of neurological deterioration.[5)-7)]

In Japan, XP-A accounts for more than half of the XP patients resulting from a founder mutation; these patients develop very severe cutaneous and neurological symptoms.[11)14)-17)] In almost 100% of XP-A patients, both the central nervous system (CNS) and peripheral nervous system (PNS) are impaired. [17)] Some studies have revealed progressive atrophy of the cerebellum, brainstem, and cerebrum starting from infancy.[17)-19)] Although It has been proposed that PNS involvement in XP is a sensory dominant axonal neuropathy, the pattern of PNS involvement and its progression with age have not been clearly delineated.[17)] In this study, we aimed to investigate the progression of PNS involvement and to clarify the overall neurodegeneration in XP-A.

Material and methods

We prospectively recruited XP-A patients referred to Kobe University Hospital Electromyography Laboratory from March, 2005 to September, 2018. All the XP-A patients were identified as having the homozygous IVS3-1 G > C mutation in the *XPA* gene using direct sequencing or polymerase chain reaction-restriction fragment length polymorphism genotyping using the restriction enzyme *AlwNI,* as previously described.[14] All XP-A patients were told to avoid sun exposure using sun cream and UV protective clothing beginning at the time of diagnosis. Twenty-two patients with encephalitis, restless legs syndrome, multiple sclerosis, epilepsy, intellectual disability, spastic paraplegia, and somatoform disorder were included retrospectively in the study as age-matched controls. These controls had no neurological signs suggesting PNS involvement.

We performed electrophysiological examinations (EP/EMG system MEB-2300, Nihon Kohden, Tokyo, Japan). Nerve conduction studies (NCS)

were performed on the right median, ulnar, and tibial motor nerves, and on the right median, ulnar, and sural sensory nerves in patients and controls. NCS were performed in all patients at diagnosis, and in 9 patients at follow-up. For motor NCS, baseline to peak amplitudes of the compound muscle action potentials (CMAPs) and motor nerve conduction velocities (MNCVs) were recorded using standard procedures. For sensory NCS, baseline to peak amplitudes of the sensory nerve action potentials (SNAPs) and sensory nerve conduction velocities (SNCVs) were recorded using antidromic stimulation. These data were analyzed using the Student's t-test or Mann Whitney U test.

We used our previously reported brain magnetic resonance imaging (MRI) volumetry data of cerebral gray matter in XP-A patients to investigate the correlation between severity of neuropathy and gray matter volume (GMV) in XP-A.[19] T1-weighted images (T1WI) (TE=3.3 ms, TR=7.2 ms, flip angle=8°, FOV=256×256 mm^2, matrix=512×512, ST=0.8 mm) were obtained using a 3-Tesla MRI scanner (Phillips Medical Systems, Eindhoven, Netherlands). T1WI were acquired with a 0.8 mm slice thickness for three dimensional (3D)

reconstructions. Images were analyzed using Statistical Parametric Mapping software (SPM12, Welcome Trust Centre for Neuroimaging, University College London, UK) working on MATLAB software (R2015a, The Mathworks Inc., Natick, MA, USA). 3D Images were segmented to gray matter using the segmentation protocol in SPM12. Total GMV were calculated using the MATLAB get_totals script (http://www.cs.ucl.ac.uk/staff/g.ridgway/vbm/) implemented for SPM.

The severity score were assessed in some of XP-A patients, according to the method previously reported.[20] The severity score of clinical manifestations in XP-A patients consists of three sections - activities of daily living, motor function and cognition – each consisting of 12, 6, and 2 items, respectively. (Section 1, activities of daily living: speech, swallowing, breathing, handling food, etc., Section 2, motor function: reflexes, contracture, standing up, gait, etc., Section 3, cognition: intellectual impairment, motivation). The score of skin manifestations in XP-A patients consists of two items - chronic and acute. For each item, the severity is scored as 0, 1, 2, 3, or 4 points, in which 0 represent no symptoms

and 4 is the most severe. Details have been published by Nakano and colleagues.[20] Brain MRI and the severity score of clinical and skin manifestations were performed concurrently within a few days with NCS.

The variance of these data was evaluated using one way ANOVA and the Kruskal-Wallis test. In accordance with the ethical guidelines of the Declaration of Helsinki, written informed consent was obtained from the guardians of all XP-A patients and controls, and studies were conducted under the protocols approved by the Institutional Review Board of Kobe University Graduate School of Medicine, Hyogo, Japan.

Results

The characteristics of patients and controls are shown in Table 1. There was no significant difference in age at the time of NCS between patients and controls. The baseline data for NCS is summarized in Table 2 and shown as box plots in figures 1 and 2. Comparisons of our control NCS data to pediatric reference ranges recently reported by Ryan et al are presented in Supplementary Tables 1

and 2). [21)]

The CMAP amplitudes of the tibial nerve were significantly lower in the XP-A group than in the control group, decreased progressively, beginning in early childhood, and could not be evoked by the age of 20 years (Fig 1A, Table 2, Supplementary fig. 1C). Median, ulnar, and tibial MNCVs were significantly slower in patients with XP-A than in the control group (Fig. 1B, Table 2). The abnormalities of CMAP and MNCV in XP-A were more prominent in the adolescent period than the childhood period and were more significant in the tibial nerve than the median and ulnar nerves. Abnormal temporal dispersion or conduction block was not identified in any nerve.[22)]

In the sensory nerves, The SNAP amplitudes of the median, ulnar, and sural nerves decreased progressively, beginning in early childhood and the sural SNAP could not be evoked by the age of 15 years. (Fig. 2A, Table 2, supplementary figure 2A, B, C). SNCVs were significantly slower in the XP-A group than in the control group (Fig 2B., Table 2).

GMV significantly declined with age ($p<0.01$). (Supplementary table 3)

There was almost no deterioration of severity score of skin manifestations. Tibial CMAPs were moderately correlated with GMV (r=0.47), and demonstrated a strong inverse correlation with severity score of clinical manifestation (r=-0.81). (Figure. 3A, B) Median and ulnar CMAPs were not significantly correlated with GMV or severity score (median: r=0.14, r=-0.33, ulnar: r=-0.14, r=-0.23, respectively).

Discussion

The results of our study are most consistent with a length-dependent sensorimotor polyneuropathy beginning in early childhood.

Neuronal loss is found throughout the brain and spine in XP-A patients.[23)-25)] Kanda and colleagues previously reported autopsy results of adult patients with XP-A showing that the number of dorsal root ganglion cells was decreased, with an accompanying loss of large myelinated fibers.[26)] The anterior horn cells were also decreased to a less severe degree and the reinnervation capacity of anterior horn cells may have been preserved.[26)] This is consistent with our

findings of mild reductions in CMAP amplitudes in the upper limbs compared with severe reductions in SNAP amplitudes. In pediatric patients with XP-A, biopsies and electrophysiological studies reveal chronic axonal degeneration, characterized by large myelinated fiber loss in sural nerve biopsies, reduced sensory and motor nerve conduction velocities, and changes of chronic denervation and re-innervation on needle electromyography.[27)-31)] Using somatosensory evoked potentials, Imai and colleagues reported that abnormalities of central conduction more severe than those of peripheral conduction[32)].

Electrophysiological changes in our study can be observed from early childhood in parallel with clinical worsening. It has been reported that children with XP-A acquire almost normal motor function, and that gait disturbance begins at approximately 12 years of age[17)]; however, we found that PNS involvement had already started in the first decade. It is speculated that neuronal degeneration of the PNS in XP-A patients starts from early childhood and contributes to a decline in the ability to perform activities of daily living. The

inconsistent correlation between GMV and NCS is probably due to the small sample size as we discuss later.

The cause of CNS and PNS degeneration in XP is still unclear. It has been said that UV radiation may not be able to reach the central nervous system and protection from the sun does not prevent neurological deterioration. [34)-37)] Therefore, it has been proposed that the neurodegeneration in XP results from accumulation of DNA damage due to endogenous oxidative stress that is normally repaired by the NER (nucleotide excision repair) system.[34)-37)] NER has two main pathways: the global genome NER (GG-NER), and the transcription-coupled NER (TC-NER).[38)39)] TC-NER or combined GG-NER and TC-NER dysfunction has been regarded as the cause of neurodegeneration in XP patients and Cockayne syndrome, which shows progressive neurological symptoms similar to XP-A. [38)-46)] However, unlike XP-A, Cockayne syndrome exhibits myelin abnormalities in the PNS, thus precluding a common pathway as the sole explanation for PNS involvement in XP-A and Cockayne syndrome.[44)-46)] Mitochondrial dysfunction is also reported to be important in neurodegeneration

in XP-A.[47] As mentioned above, the peripheral neuropathy of XP-A has been regarded as a neuronopathy, but our findings suggest postnatal length-dependent polyneuropathy that progresses over time in non-mitotic neuronal cells, of unknown pathophysiology, possibly due to mitochondrial dysfunction.

This study has some limitations. First, we used individuals with various diseases (but without peripheral neuropathy)as controls rather than healthy age-matched individuals. Second, the correlation of PNS involvement with CNS involvement was moderately weak, which differed from the correlation with severity score. This was probably due to the limited sample size.

In conclusion, we found that the electrophysiological characteristics of PNS involvement in XP-A patients are consistent with length-dependent polyneuropathy with lower limb predominance, progressing from early childhood. Both motor and sensory nerves were impaired and sensory nerves showed greater severity and progression than motor nerves. Because NCS can detect neuronal degeneration at an early age in XP patients, it can be a useful

surrogate marker for determining therapeutic effects. Further research, perhaps using animal models, is needed to better understand the underlying pathological changes in the CNS and PNS of XP-A patients.

Abbreviations

XP = Xeroderma Pigmentosum; GMV = Gray Matter Volume; UV = Ultraviolet radiation; CNS = Central Nervous System; PNS = Peripheral Nervous System; MRI = Magnetic Resonance Imaging; NCS = Nerve Conduction Studies; CMAP = Compound Muscle Action Potential; MNCV = Motor Nerve Conduction Velocity; SNAP = Sensory Nerve Action Potential; SNCV = Sensory Nerve Conduction Velocity,

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Figure legends:

Figure 1. Motor nerve conduction studies, displayed as box plots. Each parameter is analyzed using an F test, and Student's t-test is used when it is proved to be normal distribution, and Mann-Whitney U test is used when it is proved not to be normal distribution. (*: <0.05, **: <0.01, CMAP: compound muscle action potential; MNCV: motor nerve conduction velocity; P: XP-A patient; C: control; y.o.: years old)

Figure 2**.** Sensory nerve conduction studies, displayed as box plots. Each parameter is analyzed using an F test, and Student's t-test is used when it is proved to be normal distribution, and Mann-Whitney U test is used when it is proved not to be normal distribution. (*: <0.05, **: <0.01, SNAP: sensory nerve action potential; SNCV: sensory nerve conduction velocity; P: XP-A patient; C: control; y.o.: years old)

Figure 3. (A) Gray matter volume and Tibial CMAP showed moderate correlation. (B) Severity score of clinical manifestation and tibial CMAP showed negative correlation. (CMAP: compound muscle action potential, GMV: gray matter

volume)

Supplementary figure 1. Results of the nerve conduction study of XP-A patients are shown. (A) Median CMAP, (B) Ulnar CMAP, (C) Tibial CMAP, (D) Median MNCV. (E) Ulnar MNCV, (F) Tibial MNCV (CMAP: compound muscle action potential; MNCV: motor nerve conduction velocity; XP-A: group A xeroderma pigmentosum)

Supplementary figure 2. Results of the nerve conduction study of XP-A patients are shown. (A) Median SNAP, (B) Ulnar SNAP, (C) Tibial SNAP, (D) Median SNCV. (E) Ulnar SNCV, (F) Sural SNCV . (SNAP: sensory nerve action potential; SNCV: sensory nerve conduction velocity; XP-A: group A xeroderma pigmentosum)

Table 1. Characteristics of XP-A patients and controls.

	XP-A patients	Controls	p value
Number of patients and control	17	34	-
male : female	9 : 8	1 : 1	-
Age at NCS	1y2m to 21y6m （ 9y9m ± 5y0m）	2y5m to 22y8m （ 11y7m ± 6y3m）	0.16

Data are means ± standard deviation for age. Age between XP-A and controls were evaluated using Student's t-test. (NCS: nerve conduction study, y: years, m: month)

Table 2. Nerve Conduction Studies of XP-A Patients and Controls

		XP-A	control	p value	XP-A	control	p value	XP-A	control	p value	XP-A	control	p value
Age of patients and controls		0-5 years old			6-10 years old			11-15 years old			16-22 years old		
Number of patients		6	8		8	7		5	7		4	9	
Median	CMAP (mV)	6.1(4.1, 7.4)	7.4 (5.7, 8.3)	0.50	6.6 (5.7, 8.4)	7.9 (6.5, 13.2)	0.24	5.1 (3.8, 5.6)	11.8 (7.1, 13.7)	0.06	6.7 (4.7, 7.9)	9.7 (8, 11.6)	0.06
	MNCV (m/s)	45 (43, 47)	51 (49, 53)	<0.01	47 (46, 50)	59 (56, 60)	<0.01	46 (43, 48)	59 (58, 60)	<0.01	44 (37, 46)	57 (56, 61)	<0.01
	SNAP (μV)	12.4 (8.8, 21.8)	51.8 (40.2, 55.7)	<0.01	5.4 (3.7, 8.6)	64.4 (53.1, 67.0)	<0.01	2.3 (0.4, 3.4)	45.6 (34, 52.2	<0.01	0 (0, 0.45)	54.1 (34.2, 61.0)	<0.01
	SNCV (m/s)	43 (40, 45)	51 (47, 52)	<0.05	44 (43, 47)	56 (55, 58)	<0.01	36 (9, 38)	58 (58, 61)	<0.01	0 (0, 9)	63 (58, 66)	<0.01
Number of patients		6	7		8	5		5	6		4	8	
Ulnar	CMAP (mV)	5.6 (4.6, 6.3)	7.9 (6.6, 8.8)	<0.01	7.4 (6.4, 8.4)	8.9 (8.1, 8.9)	0.263	7.9 (4.6, 10.1)	9.7 (8.4, 13.2)	0.165	7.5 (6.19, 8.1)	10 (9.6, 10.6)	<0.05
	MNCV (m/s)	47 (44, 51)	53 (50, 55)	<0.05	50 (47, 55)	61 (55, 63)	<0.05	49 (46, 50)	60 (59, 62)	<0.01	45 (44, 47)	59 (57, 63)	<0.01
	SNAP (μV)	8.7 (4.8, 14.5)	36.1 (32.9, 56.35)	<0.01	3.4 (1.3, 4.5)	39.3 (30.8, 46.1)	<0.01	0 (0, 1.4)	48.6 (36.6, 49.4)	<0.01	0 (0, 2.5)	28.8 (25.8, 44.7)	<0.01
	SNCV (m/s)	41 (38, 43)	53 (47, 57)	<0.05	40 (37, 44)	54 (53, 56)	<0.01	0 (0, 36)	54 (51, 59)	<0.01	0 (0, 25)	56 (54, 61)	<0.01
Number of patients		6	9		8	6		5	6		4	7	
Tibial motor	CMAP (mV)	9.3 (8.5, 10.1)	12.6 (11.1, 15.1)	<0.05	7.7 (5.4, 10.1)	12.2 (11.7, 14.7)	<0.01	7.2 (6.7, 7.9)	11.5 (9.8, 14.0)	<0.01	4.1 (0.4, 7.2)	17.6 (14.9, 22.6)	<0.01
	MNCV (m/s)	38 (37, 40)	48 (44, 50)	<0.01	40 (39, 43)	47 (44, 51)	<0.01	37 (34, 38)	49 (46, 50)	<0.01	32 (28, 41)	46 (43, 47)	<0.01
Sural sensory	SNAP (μV)	5.8 (1.4, 9.4)	14.9 (13.9, 20.8)	<0.01	0 (0, 2.1)	21.6 (15.3, 27.9)	<0.01	0 (0, 0)	23 (20, 25)	<0.01	0 (0, 0)	20.5 (15.1, 24.3)	<0.01
	SNCV (m/s)	44 (34, 44)	49 (44, 53)	0.188	0 (0, 41)	52 (49, 54)	<0.01	0 (0, 0)	50 (48, 52)	<0.01	0 (0, 0)	48 (46, 48)	<0.01

Data are median (IQR) for parameters of nerve conduction study. Parameters between XP-A and control were evaluated using t-test. (IQR: interquartile range, CMAP: compound muscle action potential; MNCV: motor nerve conduction velocity; SNAP: sensory nerve action potential; SNCV: sensory nerve conduction velocity)

Supplementary table 1. Comparison with previous nerve conduction study by Ryan et al. (motor nerves)

		our study	Ryan et al.	our study	Ryan et al.	our study	Ryan et al.	our study	Ryan et al.
Age		2 to <5 y. o.		5 to <10 y. o.		10 to <15 y. o.		15 to <18 y. o.	
Median motor nerve	N	6	18	8	34	6	78	5	240
	CMAP (mV)	8.9 (5.3)	7.2 (1.7)	9.6 (3.9)	8.9 (2.8)	8.8 (4.1)	10.9 (2.7)	8.9 (3.1)	11.6 (2.9)
	MNCV (m/s)	53 (5)	51 (6)	54 (5)	56 (7)	52 (18)	58 (4)	60 (3)	59 (3)
Ulnar motor nerve	N	5	96	6	143	4	261	6	511
	CMAP (mV)	8.0 (2.3)	2 to <3 y. o. 6.2 (1.9)	8.5 (1.8)	9.2 (2.7)	8.5 (3.7)	10.7 (2.4)	10 (2.6)	11.9 (2.5)
			3 to <4 y. o. 7.8 (1.9)						
			4 to <5 y. o. 7.2 (1.7)						
	MNCV (m/s)	52 (5)	2 to <3 y. o. 56 (6)	56 (5)	61 (6)	56 (25)	62 (5)	62 (4)	63 (5)
			3 to <4 y. o. 58 (6)						
			4 to <5 y. o. 60 (6)						
Tibial motor nerve	N	6	56	8	119	6	274	4	414
	CMAP (mV)	12.4 (3.6)	2 to <3 y. o. 11.1 (3.1)	15 (5.2)	13 (3.8)	12 (3.6)	11.8 (3.6)	17 (2.4)	13.2 (3.9)
			3 to <5 y. o. 13.6 (5.2)						
	MNCV (m/s)	48 (4)	2 to <3 y. o. 51 (5)	47 (3)	52 (5)	43 (16)	50 (4)	46 (2)	50 (4)
			3 to <5 y. o. 50 (6)						

CMAP: compound muscle action potential; MNCV: motor nerve conduction velocity; P: XP-A patient; C: control; y. o.: years old)

Supplementary table 2. Comparison with previous nerve conduction study by Ryan et al. (sensory nerves)

		our study	Ryan et al.	our study	Ryan et al.	our study	Ryan et al.	our study	Ryan et al.
Age		2 to <5 y. o.		5 to <10 y. o.		10 to <15 y. o.		15 to <18 y. o.	
Median sensory nerve	N	6	93	8	150	6	249	5	454
	SNAP (μV)	52 (16)	2 to <3 y. o. 62 (24) 3 to <5 y. o. 54 (20)	60 (11)	55 (19)	42 (17)	50 (15)	49 (16)	56 (18)
	SNCV (m/s)	51 (4)	2 to <3 y. o. 59 (6) 3 to <5 y. o. 61 (5)	53 (6)	64 (5)	53 (19)	64 (4)	61 (6)	65 (4)
Ulnar sensory nerve	N	5	11	6	25	4	80	6	214
	SNAP (μV)	47 (22)	41 (15)	41 (7.4)	41 (15)	36 (14)	41 (12)	37 (19)	44 (17)
	SNCV (m/s)	52 (5)	65 (7)	55 (9)	65 (5)	50 (21)	67 (5)	57 (6)	67 (5)
Sural sensory nerve	N	6	24	8	46	6	95	5	165
	SNAP (μV)	17 (5)	21 (9)	22 (8.2)	21 (10)	20 (5.5)	18 (8)	18 (6.4)	21 (9)
	SNCV (m/s)	48 (6)	57 (5)	51 (7)	56 (7)	46 (16)	52 (6)	52 (4)	51 (5)

SNAP: sensory nerve action potential; SNCV: sensory nerve conduction velocity; P: XP-A patient; C: control; y. o.: years old)

Supplementary table 3. Summarized data of gray matter volume and severity score of skin and clinical manifestation at the age of nerve conduction study.

		Age of XP-A patients				p value
		0-5 y.o.	6-10 y.o.	11-15 y.o.	16- y.o.	
GMV (ml)	N	9	15	8	3	<0.01
		588.8 ± 44.7	498.3 ± 59.1	375.6 ± 34.3	225.2 ± 83.1	
Severity score of clinical manifestation	N	4	4	5	2	0.05
		20 ± 8	20 ± 5.6	35 ± 8	55 ± 26	
Severity score of skin manifestation	N	1	-	2	1	-
		5	-	6	6	

Data are means ± standard deviation for parameters of GMV and severity score of clinical and skin manifestation. Parameters of gray matter volume and severity score of clinical manifestation of each age is evaluated using one way ANOVA and Kruskal-Wallis test, respectively. (y.o.: years old, GMV: gray matter volume)

Figure 1.

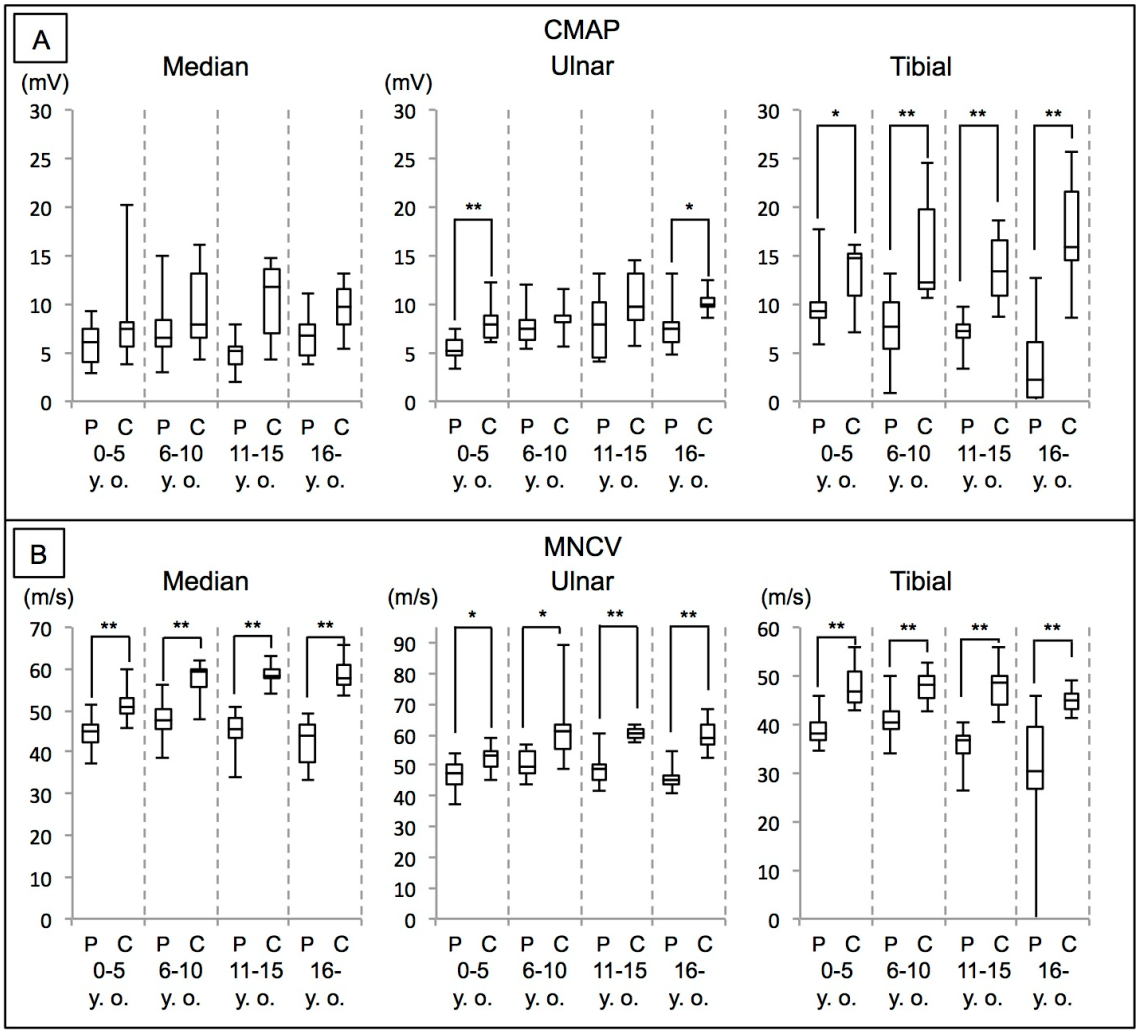

A
CMAP
Median
Ulnar
Tibial
(mV)
B
MNCV
(m/s)
P C
0-5 y. o.
6-10 y. o.
11-15 y. o.
16- y. o.

Figure 2.

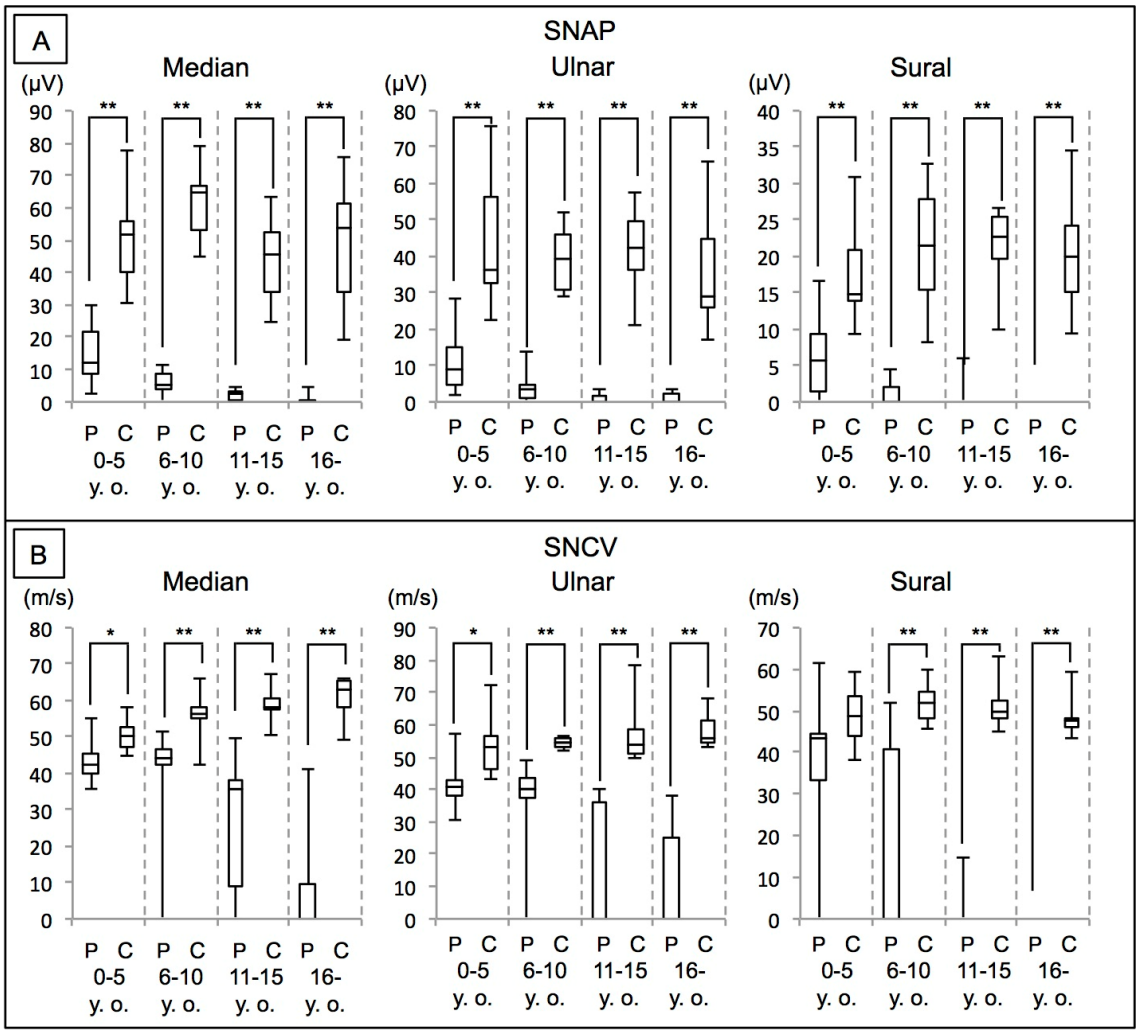
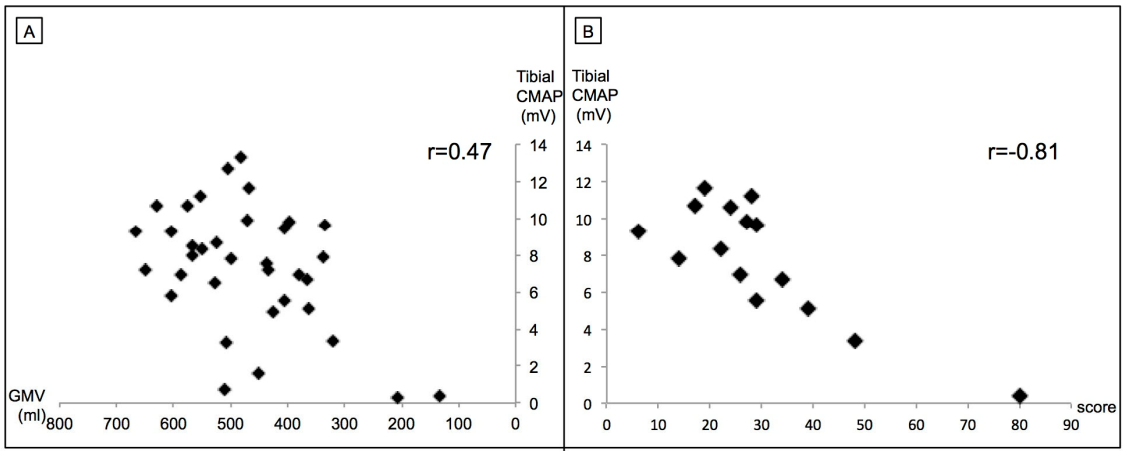
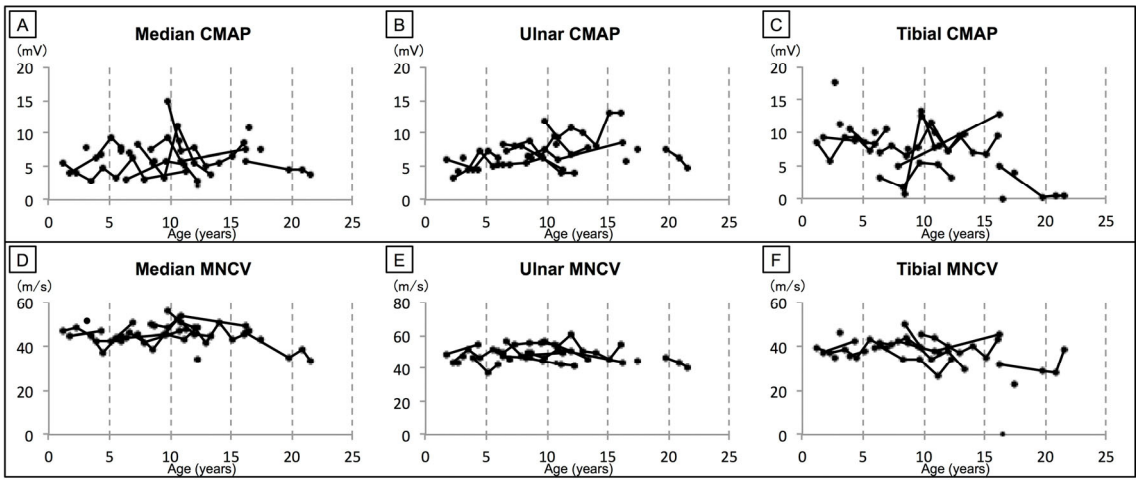


Figure 3.



Supplementary figure 1.



Supplementary figure 2.