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Commentary

Acquired and genetic channelopathies: *In vivo* assessment of axonal excitability☆

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ABSTRACT

Neuronal or axonal ion channel function can be impaired or altered in a number of disorders, such as acquired (autoantibody-mediated, toxic, and metabolic) and genetic channelopathies, and even neurodegenerative (motor neuron disease) or inflammatory diseases (multiple sclerosis, immune-mediated neuropathies). When specific channels are affected, axonal/neuronal excitability primarily alters according to original function of the corresponding channels. Separately, in the 1990s, axonal excitability testing was developed to assess ion channel function, membrane potential, and passive membrane properties non-invasively in human subjects. Using this technique, numerous papers on altered axonal excitability in a variety of disorders have been published since 2000. In a recent issue of *Experimental Neurology*, Park et al. demonstrated changes in peripheral axonal excitability in limbic encephalitis and acquired neuromyotonia with anti-voltage gated potassium channel antibodies. Unexpectedly, the results were not consistent with those caused by simple potassium channel blockade, suggesting that multiple other factors contribute to altered axonal excitability. In contrast it was reported that patients with episodic ataxia type 1 (genetic channelopathy with mutation of Kv1.1 channel gene) show prominent excitability changes exactly compatible with fast potassium channel blockade. This commentary aims to highlight findings of this study in a broader context, and provides possible explanations for the discrepancy of patterns of axonal excitability changes in acquired and genetic potassium channelopathies.

Introduction

Ion channelopathies are caused by dysfunction of channels due to hereditary or acquired disorders. Channelopathies affect almost all areas of neurological practice, including epilepsy, movement disorders, migraine, peripheral neuropathy, pain syndrome, and myopathy (Kullmann and Waxman, 2010). Over the past 2 decades, the concept of ion channelopathy has been significantly expanded. In addition to genetic channelopathies, neuronal or axonal ion channel function can be altered in a number of conditions, such as acquired (autoantibody-mediated, toxic, and metabolic) and even neurodegenerative (motor neuron disease) or inflammatory diseases (multiple sclerosis, immune-mediated neuropathies) (Krishnan et al., 2009; Kuwabara and Misawa, 2004, 2008).

Furthermore, ionic conductances are largely affected by membrane potential and trans-axonal ionic concentration. For example, in chronic dialysis patients, axons are depolarized by hyperkalemia, resulting in increased axonal sodium and potassium conductances (Kiernan et al., 2002). Conversely under hypokalemia axonal membrane is hyperpolarized, and the ionic conductances are reduced (Kuwabara et al., 2002b). Another example is diabetic neuropathy; under hyperglycemia, the activation of the polyol pathway leads to reduced Na^+/K^+ pump activity, and the resulting intra-axonal sodium accumulation decreases sodium currents due to decreased trans-axonal sodium gradient. In this regard, uremic or diabetic neuropathy is a type of channelopathy (Kitano et al., 2004; Misawa et al., 2006a,b). Therefore ionic conductances and axonal excitability are dependent on the environmental conditions, as well as the channel function itself.

Separately, an exciting development has been the identification of neurological disorders that are associated with specific antibodies to ion channels. The most common CNS syndrome associated with voltage-gated potassium channel (VGKC) antibodies is a form of limbic encephalitis (Irani et al., 2010). Another example of anti-VGKC antibody-associated syndrome is acquired neuromyotonia, also termed as Isaacs syndrome and cramp-fasciculation syndrome, that is characterized by muscle cramp, myokymia, and fasciculations due to spontaneous repetitive firing of motor axons. The motor axonal hyperexcitability is caused by suppression of fast potassium channels by anti-VGKC antibodies (Hart et al., 2002).

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In this issue of *Experimental Neurology*, Park et al. reported changes in peripheral axonal excitability in patients with limbic encephalitis or acquired neuromyotonia, whose sera had high-titer of anti-VGKC antibodies (Park et al., 2014). Axonal excitability testing was performed at the wrist of the median nerve motor axons. Patients with limbic encephalitis demonstrated prominent abnormalities in peripheral axonal excitability during the acute phase, but the pattern of excitability property changes was not consistent with blockade of VGKC, and was possibly explained by reduced sodium currents because most of the patients had hyponatremia due to a syndrome of inappropriate antidiuretic hormone secretion.

They also showed that patients with acquired neuromyotonia demonstrated no significant changes at the site of stimulation. The total findings suggest that serum anti-VGKC antibodies did not affect excitability properties at the site of stimulation (tested site), largely because the antibodies cannot assess the tested motor axons by the blood–nerve barrier (see below). The findings indicate that not only the effects of anti-VGKC antibodies, but also a complex interaction of multiple factors should be taken into consideration in the clinical situation, and therefore this study is interesting and of clinical significance.

Nerve excitability testing

Testing the excitability of axons can provide insights into the ionic mechanisms underlying the pathophysiology of axonal dysfunction in humans. The technique of threshold tracking was developed in the 1990s, to non-invasively measure a number of axonal excitability indices, which depend on membrane potential and on the sodium and potassium conductances. By delivering a conditioning stimulus, which alters membrane potential or activates specific ion channels, the current required to produce a target potential (threshold) will change. The techniques have been extensively applied to the study of the biophysical properties of human peripheral nerves *in vivo* and have provided important insights into axonal ion channel function in health and disease. This commentary focused on assessment of potassium channel function (for the details on methodology and interpretations of nerve excitability testing, please refer to previous excellent review articles [Bostock et al., 1998; Krishnan et al., 2009]).

There are many types of potassium channels on axons (Reid et al., 1999), but it is convenient, for clinical purposes, to restrict discussion to two groups that are dependent on the membrane potential, those with fast kinetics (fast potassium channels) and those with slow kinetics (slow potassium channels). Fast potassium channels are located in the juxta-paranodal region, where they contribute to the resistance of the internodal membrane and limit the depolarizing afterpotential responsible for supernormality. Slow potassium channels have a density at the node 25 times that at the internode, but their kinetics is too slow to allow them to affect the action potential directly. They help to determine the resting membrane potential, contribute to accommodation to depolarizing stimuli, and are responsible for the late subnormality. In excitability testing, the S1d phase of threshold electrotonus and supernormality are limited by fast potassium conductance, and the S2 phase and subnormality are caused by slow potassium conductance. Therefore, patterns of combined findings of the threshold electrotonus and recovery cycle can provide information about fast and slow potassium conductances (Table 1; Fig. 1).

Briefly, in the threshold electrotonus studies, the membrane potential was altered by the use of DC polarizing currents that were 40% of the unconditioned threshold. Depolarizing and hyperpolarizing currents were used, each lasting 100 ms, and their effects on the threshold current for the test motor responses were examined. The recovery cycle of axonal excitability after a single supramaximal stimulus was measured by delivering the test stimulus at different intervals after the conditioning stimulus. The intervals between the conditioning and test stimulation were changed systematically from 2 to 200 ms. When fast potassium channels are blocked, both the S1d phase and supernormality should increase (Bostock et al., 1998).

Table 1
Axonal excitability indices and potassium channel conductance.

Parameter	Ion channel
Threshold electrotonus	
S1d	(Limited by) fast potassium channel
S2	Slow potassium channel
S3	Inward rectifying channel
Recovery cycle	
Refractoriness	Recovery from inactivation of sodium channel
Supernormality	(Limited by) fast potassium channel
Late subnormality	Slow potassium channel

S1d = peak of the slow phase in the depolarizing direction, see Fig. 1.

Genetic potassium channelopathy (episodic ataxia type 1) and excitability

Detailed nerve excitability findings in episodic ataxia type 1, a representative genetic potassium channelopathy, have been reported (Tomlinson et al., 2010); episodic ataxia type 1 is a neuronal channelopathy caused by mutations in the KCNA1 gene encoding the fast potassium channel subunit Kv1.1. The disorder presents with brief episodes of cerebellar dysfunction and persistent neuromyotonia, and is associated with an increased incidence of epilepsy. The S1d phase in threshold electrotunus, and supernormality in the recovery cycle were prominently greater than those in normal controls. The findings exactly show loss of function of fast potassium channels. Using these two parameters, the patients with episodic ataxia type 1 and controls could be clearly separated into two non-overlapping groups. The authors concluded that nerve excitability testing is useful in diagnosis, since it can differentiate patients with episodic ataxia type 1 from normal controls with high sensitivity and specificity.

In a study by Park et al. (2014), the authors presumably expected the same findings, but results of actual recordings with the same techniques in patients with anti-VGKC antibodies were very different from those in patients with episodic ataxia type 1. The S1d phase of threshold electrotonus, and supernormality in the recovery cycle were smaller than those in normal controls, the opposite patterns to those of episodic ataxia type 1 (see Fig. 1 in their paper). The findings indicate that changes in axonal excitability in patients with anti-VGKC antibodies are not caused by potassium channel blocking, and other factors should have contributed to the altered excitability. The unexpected results are considered to be due to multiple factors, and the inaccessibility of the site (at the wrist portion of the median nerve) to the antibodies because of the blood–nerve barrier is one of the factors.

The blood–nerve barrier and autoantibodies

Because of the blood–nerve barrier, large molecule substances such as immunoglobulin (antibodies) cannot access the nerve trunk. The internal microenvironment in the peripheral nerves is highly regulated. In humans, this regulation is facilitated by specialized tight junction-forming endoneurial microvascular endothelial cells. The endoneurial endothelial cells come in direct contact with circulating blood and, thus, can be considered the blood–nerve barrier.

However, the blood–nerve barrier is anatomically deficient in the distal nerve terminals, nerve roots, and dorsal root ganglia (Olsson, 1990). In immune-mediated neuropathies, such as Guillain–Barré syndrome and chronic inflammatory demyelinating neuropathy, it is established that the distal nerve terminals and nerve roots, where the blood–nerve barrier is deficient, are preferentially affected (Brown

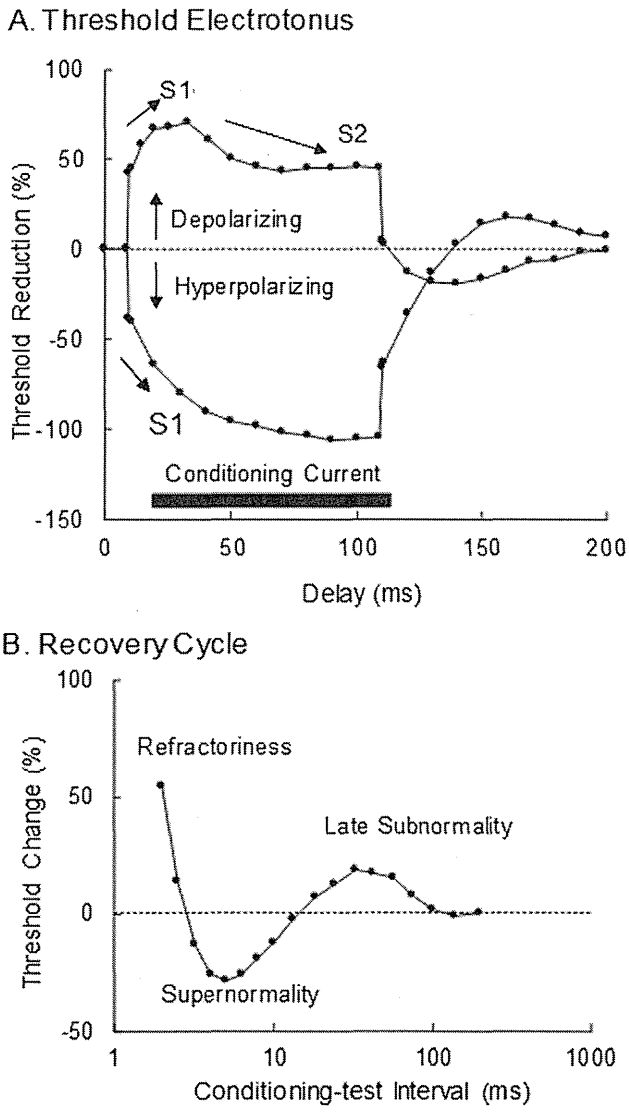

Fig. 1. Threshold electrotonus and recovery cycle measured in the median nerve at the wrist of a normal subject. A. Threshold electrotonus; changes in the threshold stimulus current for the target potential produced by subthreshold depolarizing or hyperpolarizing currents lasting 100 ms, with the intensity of the polarizing currents being 40% of the threshold. B. The recovery cycle of axonal excitability following a single supramaximal conditioning stimulus. At a short-conditioning test interval, the axons fall within the relatively refractory period, and the threshold current increases. At 3–4 ms, axons enter the supernormal period, and less current is required to activate them. Then axons enter the late subnormal period. The size of S1d and supernormality is limited by fast potassium currents, and therefore the size increases when potassium channels are impaired.

and Snow, 1991; Kuwabara et al., 2002a; Kuwabara and Yuki, 2013), and the blood–nerve barrier partly determines the distribution of demyelinative lesions. Motor nerve conduction studies frequently show prolonged distal latencies and temporal dispersion of distally evoked compound muscle action potential, suggesting demyelination in the distal nerve segments in Guillain-Barré syndrome and chronic inflammatory demyelinating neuropathy.

In anti-VGKC antibody-related disorders, the circulating antibodies can access the motor nerve terminals and roots, and fast potassium channels would be affected in these regions. Actually patients with acquired neuromyotonia in that study had motor nerve hyperexcitability evidenced by muscle cramp and fasciculations, and spontaneous motor unit activity on EMG examinations. Nerve excitability testing used in the study assesses the excitability at the stimulus site (the wrist portion of the median nerve), where blood–nerve barrier functions, and therefore anti-VGKC antibodies did not affect the tested site (nerve trunk).

Factors affecting axonal excitability

As described in the Introduction, many factors can affect axonal ionic conductances and excitability. Ion channel dysfunction itself reasonably impairs the ionic currents, but many other factors, such as membrane potential, trans-axonal ionic gradient, exposure of channels by demyelination, and increased channels in axonal regeneration, can alter ionic conductances and thereby axonal excitability.

In a paper by Park et al. (2014), altered excitability properties in limbic encephalitis patients may be caused by hyponatremia due to a syndrome of inappropriate antidiuretic hormones, and the resulting reduced trans-axonal sodium gradient and reduced sodium currents. In patients with acquired neuromyotonia, nerve excitability testing was not significantly affected by the lack of other factors influencing axonal excitability. In both cases, anti-VGKC antibodies did not affect the results. The results of this study are basically negative from the view of potassium channel blockade by autoantibodies, but sufficiently educational, telling us that in clinical practice, the determinants of axonal excitability include many other factors, some of which are secondary or co-incident, and patients show the total effects of multiple factors.

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Reconstruction Magnetic Resonance Neurography in Chronic Inflammatory Demyelinating Polyneuropathy

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To study distribution and patterns of nerve hypertrophy in chronic inflammatory demyelinating polyneuropathy (CIDP), magnetic resonance neurography with 3-dimensional reconstruction of short tau inversion recovery images was performed in 33 patients. This technique clearly showed longitudinal morphological changes from the cervical roots to the nerve trunks in the proximal arm. Nerve enlargement was detected in 88% of the patients. According to the clinical subtype of CIDP, typical CIDP patients showed symmetric and root-dominant hypertrophy, whereas Lewis–Sumner syndrome patients had multifocal fusiform hypertrophy in the nerve trunks. The patterns of nerve hypertrophy presumably reflect the different pathophysiology of each CIDP subtype.

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated neuropathy with a heterogeneous clinical manifestation.[1,2] According to the published guideline, CIDP is classified into several clinical subtypes: typical CIDP with symmetric polyneuropathy involving both proximal and distal muscles, and atypical CIDP such as multifocal acquired demyelinating sensory and motor neuropathy (MADSAM or Lewis–Sumner syndrome) and demyelinating acquired distal symmetric polyneuropathy.[2] The different clinical manifestations presumably depend on the different pathophysiology in each CIDP subtype, and several studies reported different response to immune treatments and distribution of demyelinating nerve conduction abnormalities among the subtypes.[3–5]

Magnetic resonance imaging (MRI) of nerves is becoming increasingly important in the diagnosis and evaluation of peripheral neuropathies because of its excellent soft tissue contrast and sensitivity to pathology. Previous studies have shown nerve enlargement in the nerve roots, brachial or lumbosacral plexus, and nerve trunks using T2-weighted or short tau inversion recovery (STIR) images.[6–12] However, conventional MRI provides images only of restricted regions of the peripheral nerves; coronal STIR images show a part of the nerve roots, but not peripheral nerve trunks. In 2009, a technique, termed diffusion-weighted whole body imaging with suppression of body signal, was introduced, and this technique is capable of selectively visualizing the peripheral nervous system over long trajectories.[13] Separately, reconstruction of images such as by magnetic resonance (MR) angiography is widely used in clinical practice. These advantages of MRI techniques led us to develop a 3-dimensional reconstruction of STIR images to visualize from the nerve roots to the peripheral nerve trunks, and to demonstrate nerve hypertrophy in CIDP patients.

In this study, we aimed to evaluate patterns and distribution of nerve hypertrophy along the course of peripheral nerves in CIDP, and to investigate whether the patterns of nerve enlargement are different among the clinical subtypes of CIDP.

Patients and Methods

We enrolled a total of 33 CIDP patients (25 men) seen at Chiba University Hospital between 2011 and 2013. Their condition fulfilled published diagnostic criteria.[2] Their median (range) age was 47 (22–72) years, and disease duration ranged from 1 to 28 years (median = 7.2 years). We included only typical CIDP (n = 27) and MADSAM (n = 6), and excluded

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TABLE 1. Results of Magnetic Resonance Neurography in CIDP Patients and Disease Controls

Classification	CIDP, n = 33		*p*	CMT1A, n = 6	OND, n = 25
	Typical CIDP, n = 27	MADSAM, n = 6			
Symmetric–root dominant	82%	33%	0.009	67%	0%
Multifocal fusiform	4%	67%	0.002	0%	0%
No enlargement	14%	0%	NS	33%	100%

CIDP = chronic inflammatory demyelinating polyneuropathy; CMT1A = Charcot–Marie–Tooth disease type 1A; MADSAM = multifocal acquired demyelinating sensory and motor neuropathy; NS = not significant; OND = other neurological control (amyotrophic lateral sclerosis, cervical spondylosis, and axonal neuropathy).

multifocal motor neuropathy or other variant CIDP (distal acquired demyelinating symmetric, pure motor or sensory, and focal CIDP, because of the small numbers [0 or 1]). We defined MADSAM as typical mononeuropathy multiplex or asymmetric weakness manifesting as differences in muscle strength by 1 or more Medical Research Council scale in the homonymous muscles.[3,14] Patients with Charcot–Marie–Tooth disease type 1A (n = 7) and those with other neurological disease (amyotrophic lateral sclerosis [n = 12], cervical spondylosis [n = 6], and axonal neuropathy [n = 7]) served as positive and negative disease controls, respectively. Informed consent was obtained from all patients, and the study procedure was approved by the ethics committee of Chiba University School of Medicine.

For MR neurography, a 1.5T MRI scanner (Achieva; Philips Medical Systems, Best, the Netherlands) was used. MR images were acquired from the nerve roots to peripheral nerve trunks in the upper arms with STIR sequences in the axial and coronal planes. The parameters for STIR were as follows: repetition time = 1,600 milliseconds, echo time = 200 milliseconds, field of view = 380mm, matrix = 320 × 250, slice thickness = 2.4mm, slice gap = 1 to 2mm, inversion time = 180 milliseconds. We used coronal maximum intensity projection reformatting to obtain reconstruction neurography. We classified patterns of nerve hypertrophy into (1) symmetric–root dominant enlargement, (2) multifocal fusiform enlargement, and (3) no enlargement. The classification was made by a neuroradiologist (A.S.), who was blinded to clinical information.

Statistical analyses were performed using SAS v4.3 software (SAS Institute, Cary, NC). Patterns of nerve enlargement were compared with Fisher exact test.

Results

A total of 65 patients (33 CIDP patients and 32 disease controls) were examined with MR neurography. Nerve hypertrophy was found for 29 of the 33 (88%) CIDP patients, 5 of the 7 (71%) Charcot–Marie–Tooth disease patients, and none of the 25 other disease controls (those with amyotrophic lateral sclerosis, cervical spondylosis, or axonal polyneuropathy).

In the CIDP group, the distribution pattern of nerve hypertrophy was further analyzed according to the clinical subtypes (Table1). Of the 27 typical CIDP patients, 82% showed symmetric nerve hypertrophy predominant in the cervical nerve roots, whereas 4% had asymmetric multifocal fusiform enlargement of the nerve trunk. Fourteen percent of typical CIDP patients did not have nerve hypertrophy in the territory examined. In contrast, 67% of MADSAM patients showed multifocal fusiform nerve hypertrophy in the peripheral nerve trunks.

Representative images are shown in Figure 1. The patterns of nerve hypertrophy appeared to be distinct in typical CIDP and MADSAM. The distribution of hypertrophy in typical CIDP was symmetric and predominant in the nerve roots, with gradual normalization toward the proximal arm segments distally. Nerve hypertrophy in MADSAM was asymmetric and multifocal in the peripheral nerve trunks. Neurography in a patients with left C7 radiculopathy showed presumably normal appearance of the nerve roots, brachial plexus, and peripheral nerve trunks, whereas patients with Charcot–Marie–Tooth disease type 1A had diffuse nerve hypertrophy from the cervical roots to the nerve trunks in the proximal arm segments.

The patterns of nerve hypertrophy were qualitatively similar among typical CIDP patients and among MADSAM patients. One MADSAM patient with long-standing disease (28 years) also had prominent hypertrophy of the nerve roots, but its distribution was multifocal and asymmetric (see Fig 1E). Three-dimensional displays in a patient with typical CIDP are shown in Figure 2.

In this study, clinical severity and disease duration were not associated with the presence or extent of nerve hypertrophy; presumably the timing of MRI examination was variable in the long course of the disease (eg, at relapse or during remission).

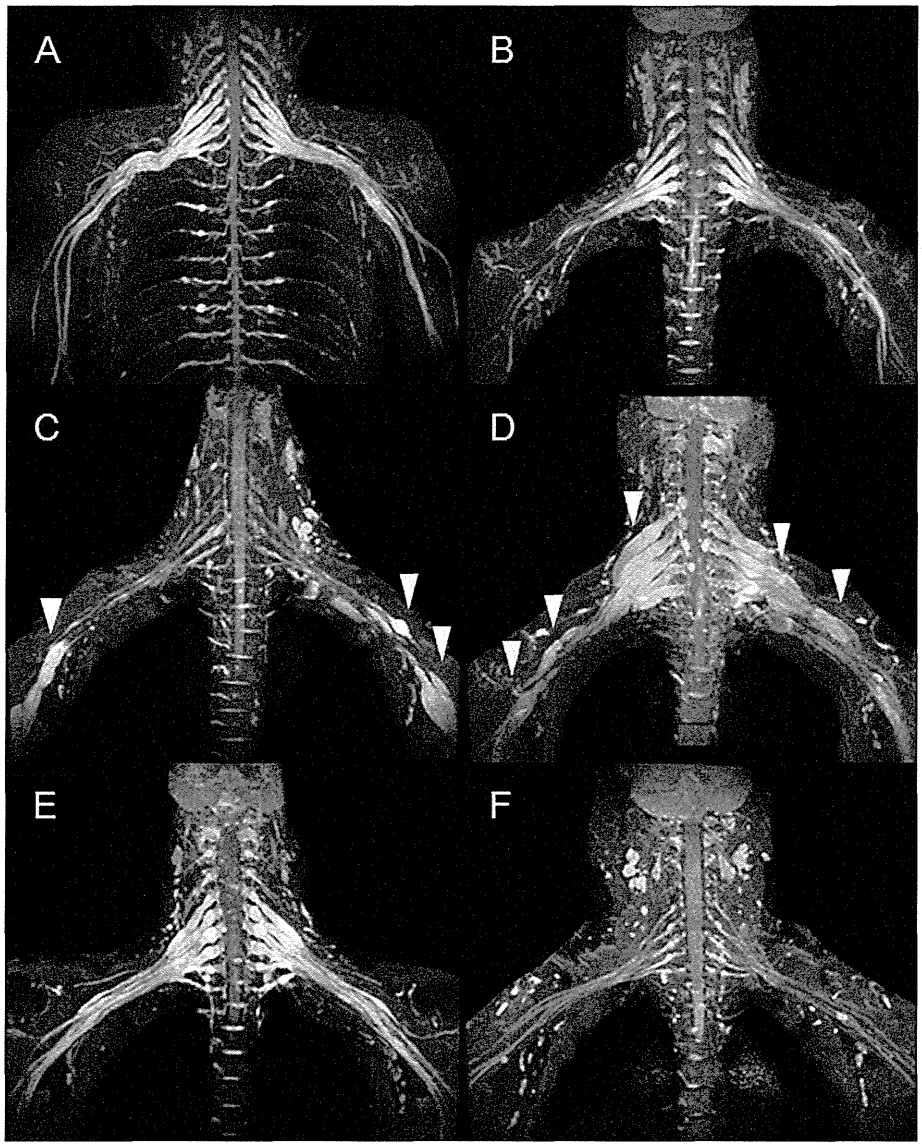

FIGURE 1: Magnetic resonance neurography with reconstruction of short tau inversion recovery (STIR) images. Maximum intensity projection images of STIR sequences in the coronal plane in typical chronic inflammatory demyelinating polyneuropathy (CIDP; A, B), multifocal acquired demyelinating sensory and motor neuropathy (MADSAM; C, D), Charcot–Marie–Tooth (CMT) disease type 1A (E), and cervical spondylosis (F) are shown. (A, B) Patients with typical CIDP 5 years (A) or 4 years (B) after onset showed prominent symmetric nerve enlargements predominant in the cervical nerve roots with gradual normalization in the proximal arm segments of the nerve trunks. (C) In a patient with MADSAM 14 years after onset, imaging revealed multifocal fusiform nerve enlargements *(arrowheads)*. (D) In an MADSAM patient (28 years after onset), multifocal fusiform nerve enlargement in the nerve roots, as well as the nerve trunks, was observed. (E) In a CMT patient (13 years after onset), imaging showed nerve hypertrophy diffusely distributed from the nerve roots to the trunks. (F) A 46-year-old man with left C7 radiculopathy. There is normal appearance from the cervical nerve roots to the nerve trunks in the proximal arm.

Discussion

Our results show the feasibility of reconstruction MR neurography with the use of STIR sequences for evaluation of peripheral nerve morphology, and different distribution patterns of nerve hypertrophy in the clinical subtypes of CIDP. Typical CIDP is characterized by symmetric hypertrophy predominantly in the nerve roots, whereas MADSAM neuropathy shows multifocal fusiform nerve hypertrophy in the peripheral nerve trunks. This is the first study to systematically assess macrographic nerve morphology over long trajectories, and to compare findings in the CIDP subtypes. The similar technique of MR neurography has been applied to other peripheral nerve diseases such as brachial plexopathy and

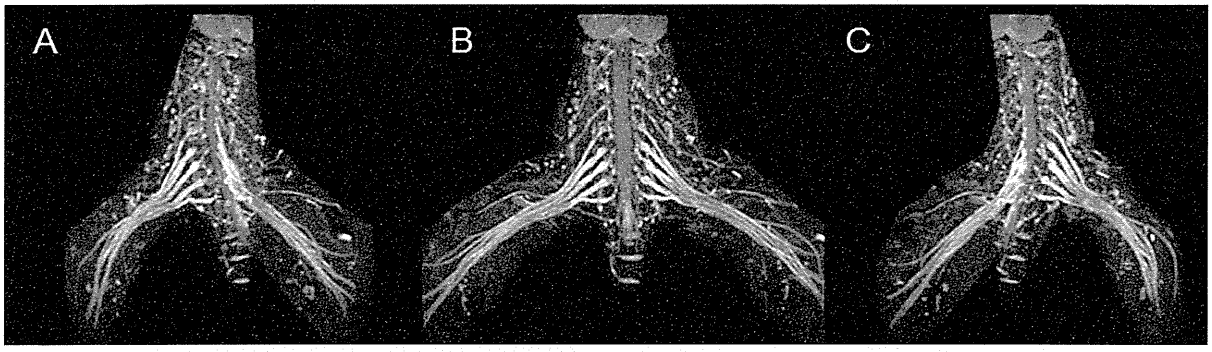

FIGURE 2: Three-dimensional displays in a patient with typical chronic inflammatory demyelinating polyneuropathy.

nerve tumor,[15] whereas reconstruction MR neurography is particularly useful for visualizing the hypertrophic peripheral nerves longitudinally, and provides new insights into the pathophysiology of each subtype of CIDP.

Typical CIDP and MADSAM are clinically defined subtypes of CIDP,[2] and the different patterns of nerve hypertrophy reflect the mechanisms of development of demyelinating lesions in each subtype. Previous electrophysiologic studies have shown that the distal nerve terminals and nerve roots, where the blood–nerve barrier is anatomically deficient, are preferentially affected in typical CIDP, raising the possibility of antibody-mediated demyelination.[3,4] In contrast, MADSAM is characterized by multifocal conduction block in the intermediate nerve trunks, and very rarely shows evidence of distal demyelination[3,12]; therefore, cellular immunity with breakdown of the blood–nerve barrier may be important. Results of our MRI study are very consistent with this hypothesis.

Specifically, nerve conduction studies are useful to examine demyelination in the distal nerve segments (eg, distal to the elbow in the median and ulnar nerves), but if nerve conduction is prominently blocked in the distal nerve terminals or forearm segments, it is difficult to detect proximal demyelination. In this regard, electrophysiology and MR neurography are complementary to investigate the whole length of a nerve.

There are several limitations in this study. First, our study did not include normal subjects, and the presence of nerve hypertrophy was determined based on comparison with controls with diseases such as amyotrophic lateral sclerosis and cervical spondylosis. Second, our evaluation was based only on visual impression, and quantitative evaluation was not performed. If combined with diffusion-weighted images, quantitative assessment at the multiple specific regions such as the nerve root, brachial plexus, and nerve trunk may be possible, and we would like to pursue this in future studies. Third, our study failed to show associations of nerve hypertrophy with clinical severity or disease duration. Longitudinal studies in individual patients from the initial progressive phase will be necessary to evaluate these factors.

As electrophysiology has shown, our results support the view that the immunopathogenesis is different in typical CIDP and MADSAM.[1,3] MR neurography may be helpful to assess the pattern of nerve demyelination and thereby the pathophysiology. Because of differing response to immune treatments in typical CIDP and MADSAM,[3,5,14] better understanding of the distribution of demyelination and of pathophysiology could provide insight into proper treatment choice.

Finally, the MR neurography method used in this study does not require a special software, and 3-dimensional reconstruction images can be obtained by exactly the same protocol as used in routine MR angiography, which is available in most of MRI laboratories. MR neurography is particularly useful for assessment of patterns of nerve hypertrophy, and will play a significant role in diagnosis and management of patients with CIDP.

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Authorship

K.S., A.S., and S.K. designed the study. K.S., S.Mis., Y.S., S.Mit., Y.I., and K.W. collected and analyzed clinical data. A.S. analyzed MRI images. A.S., S.I., H.S., H.K., T.S., H.M., and H.Y. supervised MRI analysis and interpreted the data. K.S. and A.S. drafted the manuscript. S.K. supervised this study. K.S. and A.S. contributed equally to this study.

Potential Conflicts of Interest

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