

[CASE REPORT]

Sonographic Nerve Enlargement in a Patient with Sarcoidosis

Takamasa Kitaoji, Yukiko Tsuji, Yu-ichi Noto, Shinji Ashida,
Akihiro Tanaka and Toshiki Mizuno

Abstract:

We herein report a 73-year-old woman case with sarcoid neuropathy showing nerve enlargement assessed by nerve ultrasound both before and after treatment. The site of conduction block in the left tibial nerve corresponded to the site of nerve enlargement with a hypo-echoic pattern. After treatment with prednisolone, nerve ultrasound detected the remission of the nerve enlargement, and the conduction block and clinical symptoms also improved. Nerve enlargement may reflect inflammation of the peripheral nerve. A follow-up study of sonographic nerve enlargement may be of clinical significance for assessing the effectiveness of treatment for sarcoid neuropathy.

Key words: sarcoidosis, sarcoid neuropathy, nerve conduction study, conduction block, ultrasound, nerve enlargement

(Intern Med Advance Publication)
(DOI: 10.2169/internalmedicine.5921-20)

Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology that primarily affects the lungs, eyes, liver, and skin. Sarcoidosis patients with nerve root or peripheral nerve involvement account for about 1% of total sarcoidosis cases (1). Recently, high-resolution ultrasonography has enabled us to visualize peripheral nerve morphology noninvasively (2). Nerve enlargement on ultrasound has already been reported in immune-mediated neuropathies (3-5). Regarding sarcoid neuropathy, Kerasnoudis et al. reported peripheral nerve enlargement of the ulnar nerve at the elbow (6). However, the changes in nerve ultrasound findings after treatment have not been explored.

We herein report a patient with sarcoid neuropathy showing nerve enlargement assessed by nerve ultrasound both before and after treatment.

Case Report

A 73-year-old woman became aware of paresthesia and dysesthetic pain of the right plantar surface about 9 months

prior to admission. Five months before admission, paresthesia and dysesthetic pain of the left plantar further developed. She subsequently developed drop feet on both sides, and the paresthesia extended up to the knees. Three weeks prior to admission, she became unable to walk without crutches due to lower-limb weakness.

On a clinical examination at the time of admission, her cognitive function was normal. There was no involvement of cranial nerves. The patient had asymmetric distal and proximal weakness in the lower limbs. According to the Medical Research Council scale, the muscle strength of the iliopsoas and gastrocnemius was 3/5 on both sides. The muscle strength of the hamstrings and quadriceps was 4/5 on both sides. The muscle strength of the tibialis anterior was 1/5 on the right and 2/5 on the left. There was no weakness in the upper limbs. The grip strength was 20 kg/18 kg (R/L). Tendon reflexes were absent in the lower limbs but normal in the upper limbs. She exhibited symmetric distal dominant paresthesia of the lower extremities. Pinprick and light-touch sensations were reduced below the level of the knee in both limbs. Vibration sense was diminished in both knees and ankles. The patient's autonomic function was normal.

On a blood test, the serum level of angiotensin-converting

enzyme was elevated (28.3 IU/L, normal value: 8.3-21.4 IU/L). The CSF protein level was 34 mg/dL, and the CSF cell count was 4/ μ L. Bilateral hilar-mediastinal lymphadenopathy was noted on chest X-ray and computed tomography (CT).

A trans-bronchial lung biopsy of the hilar-mediastinal lymph node showed non-caseating granulomas consistent with a diagnosis of sarcoidosis. Based on these findings, she was diagnosed with sarcoidosis. However, she exhibited no abnormality of the heart, eyes, or skin. A nerve biopsy was not performed at the patient's request.

Table. Results of Motor Nerve Conduction Studies.

	CMAP(mV)	DL(ms)	MCV(m/s)
Right median nerve	Wrist / Elbow		
Pre-treatment	6.2/6.2	3.6	57.6
After-treatment	6.1/6.0	3.2	54.9
(Reference value)	(4.0<)	(<4.0)	(54.3-63.9)
Right ulnar nerve	Wrist / Elbow		
Pre-treatment	11.5/9.4	2.6	56.7
After-treatment	8.8 / 7.1	2.6	59.0
(Reference value)	(4.2<)	(<3.1)	(55.5-67.9)
Right tibial nerve	Ankle/ Knee		
Pre-treatment	10.8 / 0.4	3.8	22.6
After-treatment	4.7/ 2.0	4.1	33.7
Left tibial nerve	Ankle / Knee		
Pre-treatment	8.8 / 0.4	5.0	26.2
After-treatment	5.1 / 2.6	4.5	36.1
(Reference value)	(7.3<)	(<5.7)	(43.9-54.2)

CMAP: compound muscle action potential, DL: distal latency, MCV: motor nerve conduction velocity

Nerve conduction studies (NCSs) were conducted on the right median and ulnar nerves and the bilateral tibial and sural nerves (Table). NCSs showed a demyelinating pattern of the tibial nerves (Table, Fig. 1A, D). The inching technique demonstrated conduction block in the left tibial nerve at a point 9-11.5 cm proximal to the ankle joint (Fig. 1A). To achieve supramaximal stimulation, we used the near nerve technique during tibial nerve stimulation with the patient's consent. F-waves were not evoked in the left tibial nerve (Fig. 1B).

We performed nerve ultrasound using the LOGIQ P5 System (GE Healthcare Japan, Tokyo, Japan) with a 12-MHz linear array transducer. The right median and ulnar nerves and bilateral tibial and sural nerves were examined. Ultrasound of the left tibial nerve showed nerve enlargement and loss of the "honeycomb" appearance with hypochoic changes inside the nerve at the site of conduction block (Fig. 2A-B) (7). The right tibial nerve had diffuse nerve enlargement in the segment between the ankle and popliteal

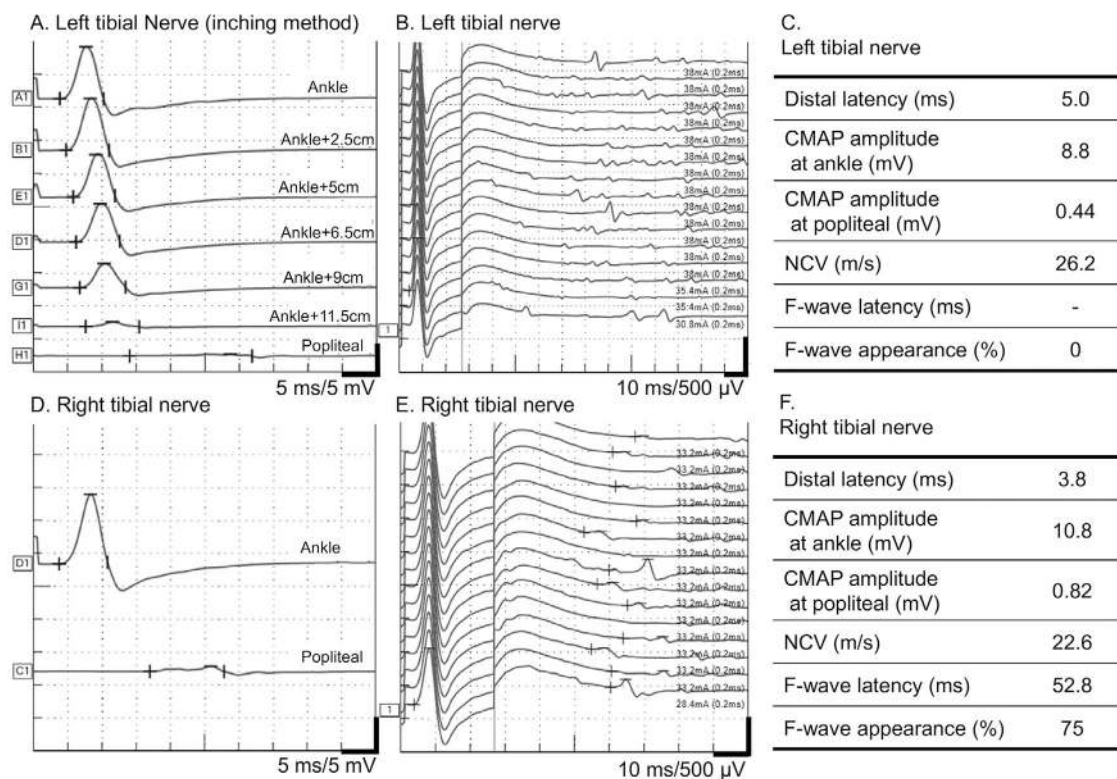


Figure 1. Nerve conduction study in the tibial nerves. Conduction block patterns were noted in both nerves when performing stimulation at the popliteal fossa (A and D). The inching technique identified conduction block in the left tibial nerve 9-11.5 cm proximal to the ankle joint (22.5-25 cm distal to the popliteal fossa). There were no distinct F-waves in the left tibial nerve (B), and F-wave latency was delayed in the right tibial nerve (E). CMAP: compound muscle action potential, NCV: nerve conduction velocity

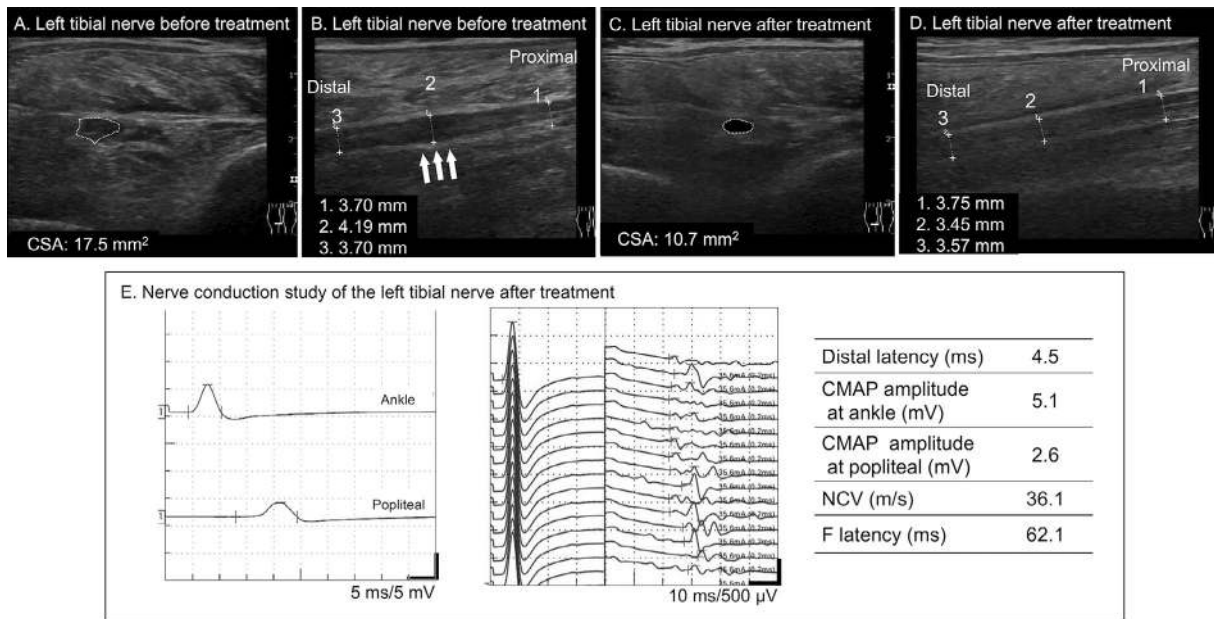


Figure 2. Ultrasound findings and nerve conduction study of the left tibial nerve before (A: cross-sectional image, B: long-axis image) and two months after (C: cross-sectional image, D: long-axis image, E: nerve conduction study) the treatment. Cross-sectional areas were measured by tracing just inside the hyperechoic rim (dotted line). The normal “honeycomb” appearance of the nerve was absent at the site showing nerve enlargement in the sectional image (A), and hypoechoic changes were noted in a long-axis view (arrow in B). The nerve enlargement, conduction block, and F wave detection rate improved after steroid therapy (C-E). CSA: cross-sectional area

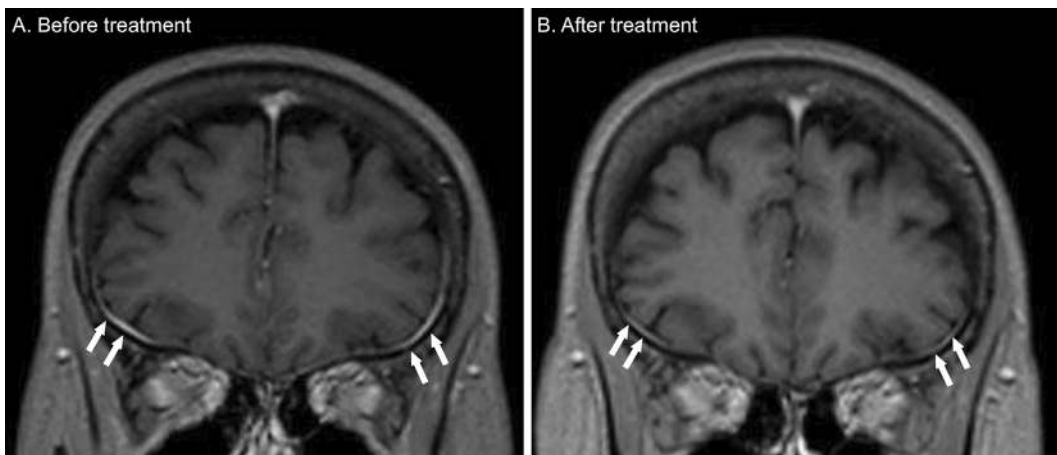


Figure 3. Coronal image of gadolinium-enhanced T1-weighted sequencing of brain magnetic resonance imaging (MRI) before (A) and one month after (B) the treatment. Dural enhancement were detected (arrow in A) and improved after the treatment (arrow in B).

fossa without conduction block on an NCS. The NCS and nerve ultrasound findings in the sural nerves and the nerves in the upper limbs were normal.

Regarding blood test findings, antinuclear antibodies, rheumatoid factor, proteinase 3-anti-neutrophil cytoplasmic antibodies (PR3-ANCA), myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA), anti-SS-A antibody, anti-SS-B antibody, human immunodeficiency virus (HIV) antibody and antigen, and tumor markers (carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and cancer antigen 125 (CA125) were all negative. There was no

abnormality in the electrophoresis of serum proteins. Gadolinium-enhanced brain magnetic resonance imaging (MRI) showed dural enhancement (Fig. 3A). Nerve root enlargement was not present on the nerve ultrasound or cervical or lumbar MRI.

Based on the results of neurophysiological tests in addition to the diagnosis of sarcoidosis, sarcoid neuropathy was suspected. High-dose intravenous methylprednisolone (HDMP: 1 g/day×3 days) followed by high-dose oral prednisolone (1 mg/kg/day) was administered 3 weeks after admission. Oral prednisolone was gradually tapered from 45 to

30 mg/day.

Five weeks after admission, her paresthesia and weakness improved, and she became able to walk without an ambulatory aid. The dural enhancement improved on gadolinium-enhanced brain MRI (Fig. 3B). Two months after admission, the demyelinating pattern on an NCS and abnormalities detected by ultrasound imaging in the left tibial nerve had also improved (Fig. 2C-E). Nerve echogenicity was assessed by a grayscale analysis. The grayscale values ranged from 0 (lowest echogenicity) to 255 (highest echogenicity). Low echogenicity of the nerve, which may indicate inflammation or edema (8), improved after treatment (mean grayscale value of the axial nerve image: from 30.2 [pre-treatment] to 37.8 [post-treatment]) at the site where the nerve cross-sectional area had been the largest before treatment.

Discussion

We herein report a patient diagnosed with sarcoid neuropathy showing treatment-responsive nerve enlargement assessed by nerve ultrasound. According to the criteria for the diagnosis of neurosarcoidosis including the peripheral nervous system (9), a definite diagnosis of neurosarcoidosis requires the pathological confirmation of sarcoidosis in nervous tissue. Although a tibial nerve biopsy was not conducted in our patient, the evidence of noncaseating granulomas in the hilar-mediastinal lymph node biopsy and the dural gadolinium enhancement on brain MRI and its improvement after treatment supported the diagnosis of neurosarcoidosis. Based on the clinical course of the patient and the presence of conduction block on NCSs, chronic inflammatory demyelinating polyneuropathy (CIDP) coexisting with silent sarcoidosis might have been a differential diagnosis. However, conduction block can be detected in sarcoid neuropathy, although a previous study showed it to be infrequent (5.3% of biopsy-proven sarcoid neuropathy showed conduction block on an NCS) (1). Focal nerve enlargement only in the left tibial nerve was not compatible with CIDP in our case, since extensive nerve ultrasound usually shows a diffuse peripheral nerve enlargement pattern in typical CIDP patients and a multiple focal nerve enlargement pattern in atypical CIDP (10, 11). Therefore, we diagnosed our case with neurosarcoidosis (diagnostic grade of probable neurosarcoidosis according to the diagnostic criteria (9)).

Regarding the mechanism underlying conduction block in sarcoid neuropathy, Said et al. suggested that conduction block was due to vasculitis-related nerve ischemia and granulomatous inflammation, as necrotizing vasculitis was observed along with granuloma (12). Furthermore, Suzuki et al. proposed the possibility of compression-induced demyelination (13). In their case, a nerve biopsy showed that sarcoid granulomas in the endoneurium caused direct compression and distortion of the nerve fiber, so they speculated that nerve compression by granulomas might induce focal demyelination as well as axonal degeneration (13). Our case showed improvement in the conduction block with a de-

crease in the compound muscle action potential (CMAP) amplitude after treatment. These findings suggest that vasculitis-related nerve ischemia and inflammation or granulomatous compression were likely resolved after treatment, although there was partial secondary axonal loss.

The cross-sectional study by Kerasnoudis et al. (6) identified peripheral nerve enlargement in patients with sarcoid neuropathy, the size of which was inversely correlated with the CMAP amplitude of the corresponding nerve. However, no previous study has described the longitudinal changes in nerve enlargement following the treatment of sarcoid neuropathy.

In the present case, tibial nerve enlargement with a hypoechoic pattern was detected at the site of conduction block. After treatment, the sonographic nerve enlargement was reduced along with the conduction block improvement (Fig. 2). This morphological and functional reversibility may reflect the pathogenesis of sarcoid neuropathy, and non-invasive morphological assessment by nerve ultrasound may be a useful method of monitoring the disease activity.

We encountered a patient with sarcoid neuropathy showing the improvement of sonographic nerve enlargement. A follow-up study of sonographic nerve enlargement may be of clinical significance for assessing the effectiveness of treatment for sarcoid neuropathy.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

John Doe (One University) edited the manuscript for non-intellectual content.

Ethical Publication Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1. Burns TM, Dyck PJ, Aksamit AJ, Dyck PJ. The natural history and long-term outcome of 57 limb sarcoidosis neuropathy cases. *J Neurol Sci* **244**: 77-87, 2006.
2. Grimm A, Heiling B, Schumacher U, Witte OW, Axer H. Ultrasound differentiation of axonal and demyelinating neuropathies. *Muscle Nerve* **50**: 976-983, 2014.
3. Beekman RVdBL, Franssen H, et al. Ultrasonography shows extensive nerve enlargements in multifocal motor neuropathy. *Neurology* 305-307, 2005.
4. Padua L, Granata G, Sabatelli M, et al. Heterogeneity of root and nerve ultrasound pattern in CIDP patients. *Clin Neurophysiol* **125**: 160-165, 2014.
5. Goedee HS, Brekelmans GJ, Visser LH. Multifocal enlargement and increased vascularization of peripheral nerves detected by sonography in CIDP: a pilot study. *Clin Neurophysiol* **125**: 154-159, 2014.
6. Kerasnoudis A, Weitalla D, Gold R, Pitarokouli K, Yoon MS. Sarcoid neuropathy: correlation of nerve ultrasound, electrophysiological and clinical findings. *J Neurol Sci* **347** (1-2): 129-136, 2014.

7. Gallardo E, Noto Y, Simon NG. Ultrasound in the diagnosis of peripheral neuropathy: structure meets function in the neuromuscular clinic. *J Neurol Neurosurg Psychiatry* **86**: 1066-1074, 2015.
8. Fisse AL, Pitarokoili K, Motte J, et al. Nerve echogenicity and intranerve CSA variability in high-resolution nerve ultrasound (HRUS) in chronic inflammatory demyelinating polyneuropathy (CIDP). *J Neurol* **266**: 468-475, 2019.
9. Stern BJ, Royal W 3rd, Gelfand JM, et al. Definition and Consensus Diagnostic Criteria for Neurosarcoidosis: From the Neurosarcoidosis Consortium Consensus Group. *JAMA Neurol* **75**: 1546-1553, 2018.
10. Grimm A, Decard BF, Axer H, Fuhr P. The Ultrasound pattern sum score - UPSS. A new method to differentiate acute and sub-acute neuropathies using ultrasound of the peripheral nerves. *Clin Neurophysiol* **126**: 2216-2225, 2015.
11. Scheidl E, Bohm J, Simo M, et al. Ultrasonography of MADSAM neuropathy: focal nerve enlargements at sites of existing and resolved conduction blocks. *Neuromuscul Disord* **22**: 627-631, 2012.
12. Said GLC, Planté-Bordeneuve V. Nerve Granulomas and Vasculitis in Sarcoid Peripheral Neuropathy: A Clinicopathological Study of 11 Patients. *Brain* 264-275, 2002.
13. Suzuki CTM, Baba M. Reversible Multifocal Conduction Block in Sarcoid Neuropathy. *J Peripher Nerv Syst* **11**: 93-95, 2006.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).

© The Japanese Society of Internal Medicine
Intern Med Advance Publication