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Letter to the Editor

# Central nervous system involvement in patients with critical illness polyneuropathy

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*Dear Editor,*

Critical illness polyneuropathy (CIP) is a common complication of severe critical illness that presents with limb and respiratory muscle weakness. The deep tendon reflex (DTR) is diminished or absent in severe forms of CIP. Herein we discuss two patients with CIP showing exaggerated DTRs. The diagnosis of CIP was based on the presence of primary axonal degeneration in sensory-motor neuropathy without any evidence of inflammation or demyelination in the electrophysiological or histopathological findings [1,2]. Brain and spinal cord magnetic resonance imaging showed no lesions which might cause the hyperreflexia in our patients. To explore the possibility of corticospinal tract involvement, a central motor conduction study using transcranial magnetic stimulation (TMS) was performed. Both patients showed delayed central motor conduction time (CMCT) and motor-evoked potentials (MEPs) with temporal dispersion (Fig. 1). This is the first case report of CIP with central nervous system (CNS) involvement not including the anterior horn cells [3]. CNS involvement may occur as part of multiorgan dysfunction and failure in the disease process underlying CIP.

## 1. Cases

### 1.1. Case 1

A 75-year-old woman with a past medical history of depression was admitted to the intensive care unit (ICU) in a regional hospital and underwent tracheal intubation due to heat stroke complicated with acute renal failure and rhabdomyolysis. Her consciousness level was E1VTM1 on a Glasgow Coma Scale without sedative agents. She recovered from a shock state within a few days (E4VTM4). Seven days after admission, muscle weakness in the upper and lower extremities appeared and progressed rapidly. She received a tracheostomy for prolonged ventilator dependence. After weaning off the ventilator, she was transferred to our hospital at 23 days after admission to the ICU. Neurological examination showed severe cognitive decline, flaccid tetraparesis with severe symmetrical muscle weakness corresponding to 0–1/5 on the Medical Research Council (MRC) scale and areflexia in all her limbs, while relative preservation of facial muscles was observed. Fiberoptic endoscopic evaluation by the otolaryngologist showed no abnormality of swallowing movement. An electroencephalogram showed diffuse slow waves ranging from slow alpha to theta without epileptiform discharges. Three months after the onset of initial symptom, she showed exaggerated DTRs for the first time with limited recovery of muscle strength but no other sign of upper motor neuron dysfunction. Follow-up brain MRI showed diffuse brain atrophy but no focal lesion. Severe cognitive impairment remained. She was thought to have long-term cognitive impairment after crinical illness.

### 1.2. Case 2

A 67-year-old woman with a past medical history of schizophrenia was admitted to the ICU in a regional hospital due to septic shock caused by an infection in the urinary tract. Although she recovered from the sepsis, she suffered from muscle weakness in her extremities and was transferred to our hospital at day 45 after the onset of initial symptom. On neurological examination, the patient was fully alert and showed no evidence of cognitive decline or respiratory muscle weakness. Her speech was normal. She showed flaccid type, severe symmetrical muscle weakness (upper limbs 2/5 and lower limbs 1/5 on the MRC scale) with preservation of facial muscles and exaggerated DTRs in all her limbs. The hyperreflexia was noticed for the first time, but there was no other sign of upper motor neuron dysfunction. A stocking distribution decrease in appreciation of superficial sensation and pain was identified in both legs. Vibration sensation was decreased in all extremities.

## 2. Neurophysiological studies and biopsy findings

In both patients, NCS and needle electromyography revealed symmetrical, length-dependent axonal polyneuropathy with reduced compound muscle action potential and sensory nerve action potential amplitudes, preservation of sensory and motor conduction velocity and active denervation potentials predominantly in the distal muscles. Sural nerve and peroneus muscle biopsies in both patients showed features of sensory-motor axonal neuropathy with a reduction in large diameter

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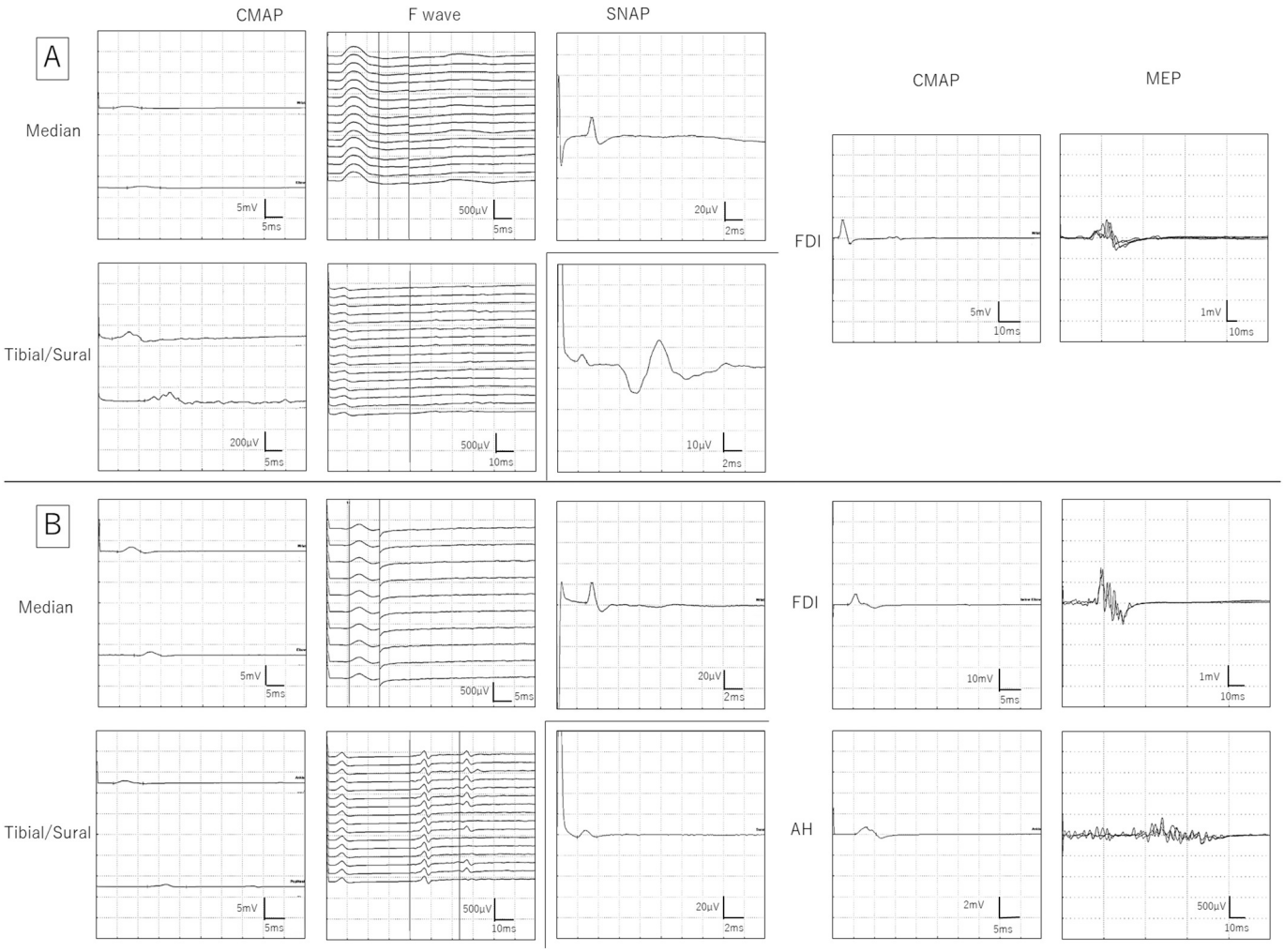


**Fig. 1.** Findings of the nerve conduction study and transcranial magnetic stimulation in Cases 1 (A) and 2 (B).
AH, abductor hallucis muscle; CMAP, compound muscle action potential; FDI, first dorsal interosseous muscle; MEP, motor evoked potential; SNAP, sensory nerve action potential.
MEPs were obtained from contracted muscles 7 and 3 months after the onset of initial symptom in Cases 1 and 2, respectively. The CMAP and F wave were recorded from the FDI and AH muscles by electrically stimulating the ulnar and tibial nerves. Then, the MEPs were recorded with surface electrodes from the same muscles by TMS. TMS was performed both at rest and during voluntary contraction for each muscle using Magstim 200 (Magstim Co. Ltd., UK) and a figure-of-8 coil. MEP latencies were measured to the first negative deflection. The CMCT was calculated using the following formula: MEP latency – (CMAP latency + F wave latency – 1)/2. The MEP latency during contraction was used to calculate the CMCT. The filter setting was 5 Hz to 5 kHz both for the nerve conduction study and the TMS study. In Case 1, the CMAP for FDI was diminished while the CMAP of AH was not able to be evoked. The MEP for FDI showed temporal dispersion, and the MEP for AH was absent. The CMCT for FDI was prolonged (8.1 ms; normal range 3.8–7.9 ms). In Case 2, the CMAPs for both FDI and AH decreased. The MEP for FDI showed temporal dispersion and the CMCT was prolonged (8.7 ms). The MEP for AH also showed temporal dispersion with decreased amplitude, but the CMCT was within the normal range (13.5 ms; normal range: 14.5–18.4 ms).

myelinated fibers, scattered myelin ovoid formation and scattered atrophic angulated myofibers. TMS was performed at 7 and 3 months after the onset of initial symptom in Cases 1 and 2, respectively, and revealed delayed CMCT (for FDI, 8.1 ms in Case 1 and 8.7 ms in Case 2; noramal range 3.8 - 7.9 ms) and MEPs with temporal dispersion (Fig. 1). Neither case had evidence of history or imaging of related pathology that could have explained abnormalities in the TMS study.

## 3. Discussion

Guillain-Barré syndrome (GBS) is a form of acute inflammatory polyneuropathy characterized by rapidly progressive symmetrical weakness and areflexia. There are reports, however, of hyperreflexia in patients with the axonal form of GBS [4,5]. This condition needs to be considered in the differential diagnosis of CIP in our patients.

Although it was difficult to differentiate GBS from CIP clearly, none of the findings, including the presence of autoantibodies against gangliosides, suggested GBS in our patients [6,7]. In GBS cases with hyperreflexia, delayed CMCT was transiently observed before treatment [5]. In contrast, in our patients, delayed CMCT was observed at several months after the onset of initial symptom. GBS is the primary neurological reason of admission on the ICU, whereas CIP develops during a patient's stay on the ICU for another reason. The clinical findings, together with the patient's history, were more compatible with CIP.

Aggressive treatment of sepsis and multiple organ failure is considered the most effective method of reducing CIP incidence [1,2]. These findings suggest that CIP is not an isolated event, but rather is an integral part of the process leading to multiorgan dysfunction and failure. The present cases provide further evidence of multiorgan involvement including the CNS in the disease process associated with CIP and corroborate the concept of shared microcirculatory, cellular, and metabolic pathophysiological mechanisms in CIP [1].

Recent studies indicate a high prevalence of long-term cognitive impairment among survivors of critical illness [8]. This type of

encephalopathy often occurs with concomitant CIP as seen in Case 1, and might have contributed to some of the motor manifestations in our patients. In addition to peripheral nervous system, damage to the central motor system may attribute to the poor functional prognosis of neuromuscular weakness in CIP. Further a large-cohort study examining central motor conduction in patients with CIP will confirm our findings and reveal its relationship to the prognosis.

## Declarations of interest

The authors declare no conflicts of interest.

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Aki Murayama*, Keizo Sugaya, Toshio Shimizu, Yoko Sunami, Shinsuke Tobisawa, Eiji Isozaki
*Department of Neurology, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan*
*E-mail address:* aki_murayama@tmhp.jp (A. Murayama).

* Corresponding author at: Department of Neurology, Tokyo Metropolitan Neurological Hospital, 2-6-1 Musashidai, Fuchu, Tokyo 183-0042, Japan.