

## Case Report



# An Exploration of the Neural Network of Lance-Adams Syndrome: a Case Report

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## HIGHLIGHTS

- We used transcranial magnetic stimulation (TMS) and diffusion tensor imaging (DTI) to explore the neural network of Lance-Adams syndrome (LAS).
- Gamma-aminobutyric acid type B (GABA<sub>B</sub>)-mediated inhibition was decreased on TMS.
- There were significant changes in some diffusion metrics on DTI.

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# An Exploration of the Neural Network of Lance-Adams Syndrome: a Case Report

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### Conflict of Interest

The authors have no potential conflicts of interest to disclose.

## ABSTRACT

Lance-Adams syndrome (LAS) is a rare neurological disorder that may occur after cardiopulmonary resuscitation. The LAS is usually caused by hypoxic changes. Neuroimaging studies show that the brain pathology of LAS patients is not uniform, and the pathophysiology of the myoclonus can vary from patient to patient. Our case study contributes to this etiological heterogeneity by neuroimaging and transcranial magnetic stimulation (TMS). In patients with rare brain conditions such as LAS, a combination of brain stimulation methods, such as TMS, and diffusion tensor imaging can provide insights into this condition's pathophysiology. These insights can facilitate the development of more effective therapies.

**Keywords:** Hypoxic Brain Damage; Myoclonus; Transcranial Magnetic Stimulation; Diffusion Tensor Imaging

## INTRODUCTION

Lance-Adams syndrome (LAS) is a rare neurological disorder. The number of LAS diagnoses is expected to grow as emergency medicine progresses, and more patients survive cardiac arrest [1]. The underlying pathophysiological mechanism of LAS remains elusive. Some studies have suggested that post-hypoxic myoclonus originates from the subcortical and cortical structures [2,3]. In this study, we aim to explore the neural network related to the myoclonus and explore the patient's cortical physiology using diffusion tensor imaging (DTI) and paired-pulse transcranial magnetic stimulation (TMS). The aim is to study the underlying pathophysiological mechanism of LAS. Here we present a case report of one patient diagnosed with LAS.

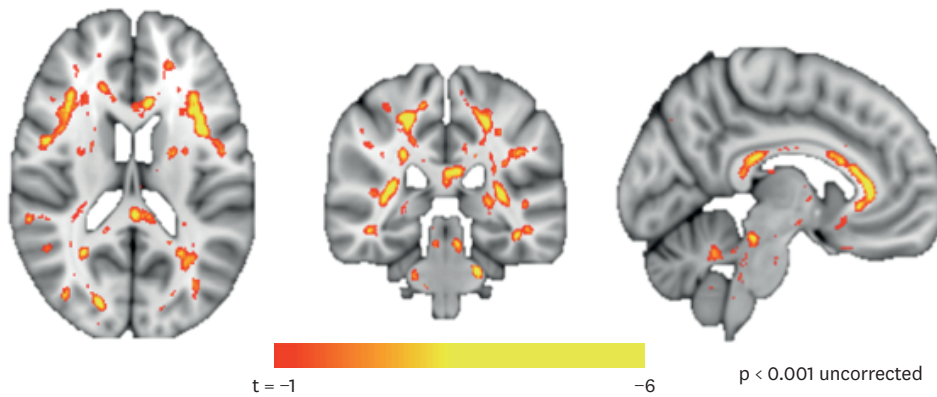
## CASE REPORT

A 69-year-old man was admitted to our hospital for proper rehabilitation on continuous myoclonus appeared after a successful cardiopulmonary resuscitation (CPR) 6 months ago. He underwent a cardiac arrest 6 months ago, and his sinus rhythm returned after 9 minutes

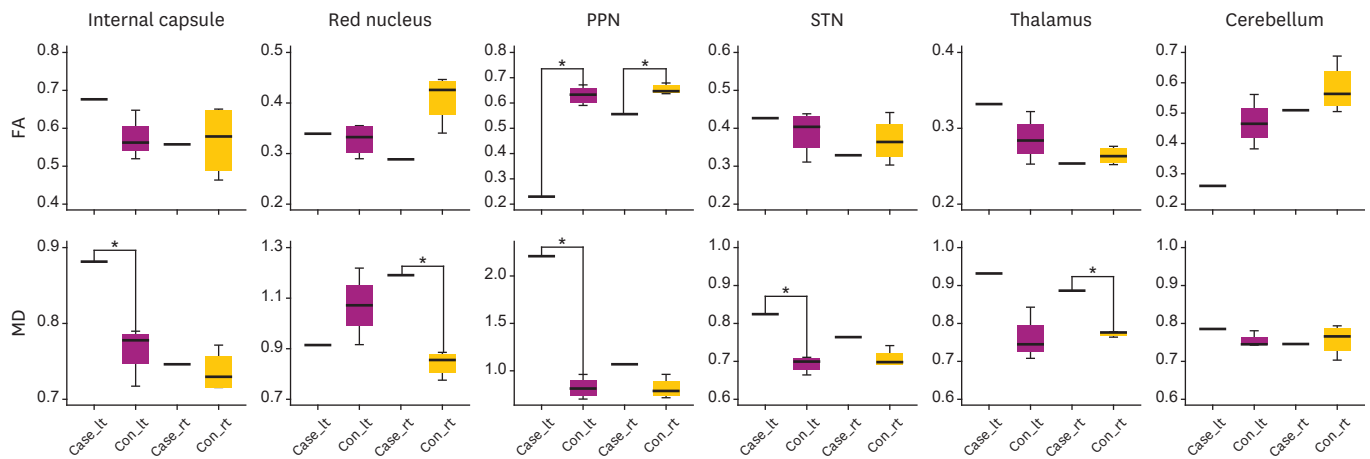
of CPR. After 10 days, he experienced intermittent myoclonic jerks while he was in the intensive care unit (ICU). He received pharmacological management such as levetiracetam, valproate, piracetam, clonazepam, and oxiracetam. On admission to our hospital, the neurological examination, paired-pulse TMS, and DTI was performed on him. His muscle power was good in all extremities based on a manual muscle test. However, he could not maintain a sitting posture and walk independently due to myoclonic jerks and balance problems. Spasticity and deep tendon reflexes were normal in all extremities. He scored a 22 on the Korean version of the Mini-Mental Status Examination with memory impairment. Considering the good clinical course and delayed onset along with regained consciousness within a short time, in this case, we could exclude myoclonus status epilepticus [4].

For paired-pulse TMS, a Magnetic Stimulator STM 9000 (ATES MEDICA Device, Verona, Italy) was used to deliver biphasic pulses with current flowing in the brain in an antero-posterior and then a postero-anterior (AP-PA) direction. The paired-pulse TMS was measured according to the recommendations of the International Federation for Clinical Neurophysiology [5]. First, we checked the resting motor threshold (RMT) 48% on the left primary motor cortex (M1) and 47% on the right M1. The single-pulse TMS was administered at 120% of RMT over bilateral M1. Second, we used 3 paired-pulse paradigms in the bilateral M1s to observe the cortical physiology. Short intracortical inhibition (SICI) was composed of a subthreshold conditioning stimulus (CS; 90% of RMT) and a suprathreshold test stimulus (TS; 120% of RMT) with an inter-stimulus interval (ISI) of 3 ms. In intracortical facilitation (ICF), CS and TS settings were the same with ISI of 12 ms. Long intracortical inhibition (LICI) was obtained using a suprathreshold CS (120% of RMT) and a suprathreshold TS (120% of RMT) with ICI of 100 ms. Ten motor evoked potentials (MEPs) were collected for each single-pulse and paired-pulse TMS protocol. We calculated the mean amplitudes. The mean MEPs amplitude of single-pulse TMS, SICI, ICF, and LICI in the right M1 was  $1.338 \pm 0.350$  mV,  $1.208 \pm 0.304$  mV,  $1.886 \pm 0.619$  mV, and  $4.431 \pm 0.741$  mV, respectively. The mean MEPs amplitude of single-pulse TMS, SICI, ICF, and LICI in the left M1 was  $1.521 \pm 0.268$  mV,  $1.144 \pm 0.305$  mV,  $1.720 \pm 0.110$  mV, and  $4.466 \pm 0.428$  mV, respectively. The results showed that the amplitude of SICI decreased whereas that of ICF increased. However, the amplitude in LICI did not decrease but instead increased. LICI is related to gamma-aminobutyric acid type B (GABA<sub>B</sub>)-mediated inhibition [6,7].

DTI was acquired using a diffusion-weighted, echo-planar imaging sequence (repetition time [TR] = 5,000 ms; echo time [TE] = 100 ms; slice thickness = 2.2 mm; no gap; in-plane resolution =  $2.4 \times 2.4$  mm, 32 independent diffusion gradient directions using  $b = 1,000$  sec/mm<sup>2</sup>). DTI data were analyzed using FMRIB's Diffusion Toolbox from the FMRIB Software Library (Oxford, UK), described in [8]. We performed a voxel-wise comparison between the case and controls using tract-based spatial statistics (TBSS) [9]. For precise extraction of the diffusion metrics from the same region of interests (ROIs), the ROIs were acquired from the standard space using the atlas provided by FSL software, projected to individual space using the inverse transformation matrix. Then, fractional anisotropy (FA) and mean diffusivity (MD) values were extracted from individual subjects' ROIs. Modified t-test for single-case analysis was performed using computer program Singlims\_ES.exe. to compare the data of the patient with controls [10]. TBSS results showed a widespread decrease in white matter volume compared to healthy controls of the same age (4 controls, average age:  $69.5 \pm 3.3$ , M:F = 2:2) (uncorrected  $p < 0.001$ ) (Fig. 1). We observed a significant decrease in FA in several areas of the brainstem. Further, we analyzed the ROIs related to myoclonus (red nucleus, subthalamic nucleus [STN], thalamus, and cerebellum), including gait performance (the



**Fig. 1.** Diffusion tensor imaging-tract-based spatial statistics analysis showed significant areas in the patient compared with those in the controls. White matter structures showing a significant fractional anisotropy decrease in different brain regions in the patient ( $p < 0.001$  uncorrected). Statistical images were overlapped onto the MNI152 template (gray-scale) for visualization.



**Fig. 2.** The diffusion metrics in the regions of interest in the myoclonus-related network (red nucleus, subthalamic nucleus, thalamus, and cerebellum) and the mesencephalic locomotor center (pedunculopontine nucleus) showed decreased FA and increased MD in the pedunculopontine nucleus and increased MD of the right red nucleus, thalamus, and left subthalamic nucleus (compared to controls). FA, fractional anisotropy; MD, mean diffusivity; PPN, pedunculopontine nucleus; STN, subthalamic nucleus. \* $p < 0.05$ .

mesencephalic locomotor center: pedunculopontine nucleus [PPN]). The results showed that FA decreased and MD increased in the PPN and increased MD of the right red nucleus, thalamus, and left STN (compared to controls) (Fig. 2). This case study was approved by the local Institutional Review Board.

## DISCUSSION

This case demonstrated changes in the myoclonus-related network's diffusion metrics along with the mesencephalic locomotor region in the subcortex and brainstem parallel to diffuse injury in the cerebral white matter with decreased GABA<sub>B</sub> mediated inhibition.

The neurotransmitters, including serotonin and GABA, are related to LAS [11]. Our paired-pulse TMS results showed that the cortical pathology related to intracortical GABA<sub>B</sub> mediated inhibition dysfunction would be in line with LAS's mechanism. However, we did not control

medication during paired-pulse TMS, although many antiepileptic drugs could have various effects on cortical excitability. Among them, clonazepam, a type of benzodiazepine, which acts on GABA<sub>A</sub> receptors to reinforce GABA action, can increase SICI and decrease ICF [12]. Levetiracetam, which acts on glutamatergic transmission, can decrease the MEP recruitment despite mixed results on RMT [12]. Valproate, which affects voltage-gated sodium channels, can increase the MEP threshold and decrease MEP amplitude via membrane excitability [12]. Therefore, careful consideration is needed for the interpretation of the paired-pulse TMS results in this case.

In adults, mild to moderate hypoxic-ischemic brain injury leads to watershed infarcts. Severe injury affects the gray matter of the perirolandic cortical neurons, occipital cortex, medial prefrontal cortex, basal ganglia, thalamus, hippocampus, and cerebellum [13]. In the acute stage (less than 24 hours), the affected cortex and deep gray matter may show restricted diffusion in the form of a bright signal on diffusion-weighted images due to cytotoxic edema [14]. Compared to magnetic resonance imaging (MRI), whole-brain-white-matter-voxel-based morphometry, such as TBSS, was sensitive in detecting decreased white matter integrity, which showed not only the white matter of the cerebral cortex but also many significant areas in the brain stem whereas this case showed no significant change in the conventional MRI.

The pathophysiology of LAS has not been clearly defined. Pontine tegmentum, mesencephalon, ventrolateral thalamus [15], temporal lobe [11], basal ganglia [16], cerebellum [17,18], hippocampus [19], and frontal lobe [19] have been discussed in various imaging studies, including MRI, positron emission tomography, single-photon emission-computed tomography. The cerebellum and thalamus are possible candidates for the pathogenesis of post-hypoxic myoclonus, which often have a lesion in hypoxic insult. The repetitive firing of thalamo-cortical fibers arising from the ventrolateral nucleus, the central relay nucleus from the cerebellum to the sensory-motor cortex, was proposed as one mechanism of myoclonus in LAS [20]. Besides, dentato-rubro-olivary circuit (Guillain-Mollaret triangle) is associated with the pathogenesis of palatal myoclonus. A lesion in the circuitry between the olivary nucleus, red nucleus, and sometimes deep cerebellar nuclei can cause myoclonus. We further explored the ROIs that are related to myoclonus, including the mesencephalic nucleus, PPN, which would be a unique finding of this case. The ROI analysis results demonstrated the subcortical pathology involving the red nucleus, closely connected to the inferior olivary nucleus and cerebellum. It is possible that the cerebellar lesion initiated the process that disrupted of pathways linking the cerebellum to the thalamus and STN. The PPN pathology might be an epiphenomenon because he could not perform independent gait for almost six months because of myoclonus.

In application, the most significant contribution of this case study was to delineate possible etiological heterogeneity of LAS. In patients with rare brain conditions such as LAS, a combination of functional neuroimaging such as TMS and DTI can provide insights into the pathophysiology of this condition. These insights can facilitate the development of more effective therapies.

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