

## CASE REPORT



# Long-term physical therapy for neuropathic pain after cervical spinal cord injury and resting state electroencephalography: a case report

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**INTRODUCTION:** Neuropathic pain after spinal cord injury is difficult to treat, and it is associated with abnormalities in the function of the thalamus-to-cortex neural circuitry. Aerobic exercise provides immediate improvement in neuropathic pain and is associated with abnormal resting electroencephalography (EEG) findings in patients with spinal cord injury. This study aimed to investigate whether physical therapy, including walking, can improve neuropathic pain and EEG peak alpha frequency (PAF) in the long term in a patient with cervical spinal cord injury.

**CASE PRESENTATION:** A 50-year-old man was admitted with a cervical spinal cord insufficiency injury sustained one week prior. The residual height was C5. Neuropathic pain was observed in the fingers bilaterally. A numerical rating scale (NRS) was evaluated to measure the weekly mean and maximum intensities of pain. Resting EEG was measured, and the PAF was calculated. Each time point was evaluated in 2-week intervals from the time of admission, and the rate of change ( $\Delta$ ) of PAF was calculated based on the initial evaluation. Interventions included 18 weeks of standard physical therapy focusing on gait, with additional intensive gait training (4–10 weeks). The NRS scores for the mean and maximum intensities of pain decreased significantly after 6 weeks, and  $\Delta$ PAF increased significantly after 4 weeks. Improvement in PAF coincided with the start of intensive gait training.

**DISCUSSION:** PAF shifts to a high frequency during intensive gait training, suggesting the effectiveness of aerobic exercise. Furthermore, there is a close relationship between PAF, pain, and the quantification of pain changes.

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## INTRODUCTION

After spinal cord injury (SCI), neuropathic pain (NP) is known to occur in addition to motor and sensory paralysis and autonomic disorders [1], and its prevalence ranges from 50–90% in patients with SCI [2–4]. NP is intractable, limits daily life activities, and negatively affects psychological indicators such as quality of life and mood [5–7]. Therefore, interventions aimed at providing analgesia for NP are important for the rehabilitation of patients with SCI.

Interventions for NP after SCI include walking and aerobic exercise (AE) [8–10], noninvasive brain stimulation [11], visual illusions [12], and cognitive behavioral therapy [13]. AE has been shown to increase the pain threshold [14], and it is easy to implement in clinical practice. We have previously reported that AE with wheelchair propulsion can temporarily reduce pain intensity in patients with SCI [15]. However, our report was limited to single-session validation, and the effects of longitudinal AE remain unclear.

NP is generally assessed using paper-based evaluations, such as the numerical rating scale (NRS) and visual analog scale. Studies examining brain activity in patients with NP have proposed that it can be quantitatively assessed by measuring resting electroencephalography (EEG) and by calculating the peak alpha frequency (PAF) [16, 17].

PAF is thought to reflect thalamocortical dysrhythmia, a dysfunction of the neural circuitry between the thalamus and cerebral cortex, which is thought to be one of the causes of NP [16–18]. Moreover, PAF has been shown to shift to a lower frequency range in the presence of NP [15–17]. In our previous study, PAF in the parietal area of patients with SCI and NP was at a lower frequency range (~1 Hz) than that of healthy individuals [15]. On the other hand, it has been reported that PAF is deflected to the high-frequency range by AE [19]. We found that PAF was deflected to the high-frequency range and that pain intensity was reduced after AE in patients with SCI and NP [15].

This case report aimed to determine whether physical therapy, including intensive gait training, can improve pain intensity and PAF in the long term in patients with cervical SCI and NP.

## CASE PRESENTATION

The patient was 50-year-old man. His job was as a heavy equipment operator, and he lived alone. The patient was healthy and did not have any pain. He fell from a height and was diagnosed with non-osteoporotic cervical SCI. Therefore, no surgical treatment was performed. He was admitted to a rehabilitation hospital with a cervical SCI in sufficiency injury

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sustained 1 week prior. The neurological level of the International Standards for Neurological Classification of SCI (ISNCSCI) was C5, and the Impairment Scale was D. The motor score at admission was 88, and the sensory scores for both touch and pinprick were 212. The location and subjective intensity of pain were assessed using the NRS. There was strong prickling pain in the fingers bilaterally, with a maximum NRS score of 8 and a mean score of 7. The patient had NP of at-level in the International Spinal Cord Injury Pain Classification [20], pain and allodynia in both fingers throughout a day, and severe pain when objects came into contact with the fingers. As a result, the patient had trouble manipulating objects with his fingers in his daily life. NP was determined to be positive with a score of 5 using the Japanese version of DN4 [21]. He had no other pain, except NP. Walking ability and walking independence were 0.62 m/s and a score of 4, as assessed by the 10-meter walking test and Walking Index for SCI II (WISCI II), respectively. The patient was using a wheelchair for transportation within the hospital at the time of admission.

Physical therapy was conducted for at least 40 min per session, 7 times per week, for 18 weeks. Standard physical therapy included strengthening of limb muscles and gait training, and was carried out step-by-step using parallel bars, a walker, a clutch, and independent gait. From weeks 2–10 of intervention, intensive gait training was conducted by adding body weight support treadmill training to standard physical therapy. During 10 weeks, the intervention focused on standard physical therapy and walking. Body weight support training was performed by supporting 30% of the body weight. The load was adjusted incrementally according to the patient's gait condition to achieve a "somewhat hard" load in terms of subjective exercise intensity, and the walking speed was adjusted within the parameter of 2 to 5 km/h for 20 min during one session. For medication, the patient was only taking pregabalin to reduce pain after injury, which did not change throughout the intervention period.

Resting EEG was measured for 3 min with the eyes closed using a 1-channel electroencephalograph (Brainpro; Futek Electronics Co., Ltd., Yokohama, Japan). Electrodes were placed at C3 and C4, which are considered to be the regions corresponding to the left and right primary motor cortex, based on the international 10–20 method of EEG measurement.

The sampling rate is 512 Hz and the bandpass filter is 0.5–70 Hz. The measured EEG data were subjected to power spectrum analysis using MATLAB (Welch's power spectrum density estimation: 1 segment is 2 seconds, 1 second overlap) to find the frequency with the largest amplitude in the range of 7–14 Hz and

to calculate the center of gravity of each channel [22, 23]. The average of both channels was then calculated.

Each measurement was performed at 2-week intervals, beginning from the assessment at admission, for 18 weeks. For PAF, the rate of change ( $\Delta$ ) for each week was calculated based on the assessment at admission. The site of pain was assessed every 8 weeks. The 10-meter walking test was performed from the second week onwards because walking was difficult at the time of admission.

Table 1 presents the evaluation results. Both the mean and maximum NRS scores decreased significantly from 2–8 weeks, and the pain did not worsen significantly thereafter. Additionally, the location of pain was limited to the distal part of the fingers.  $\Delta$ PAF increased significantly at 4 weeks and decreased at 10 weeks, but it remained increased compared to the value at admission thereafter until 18 weeks. The improvements in NRS score and PAF coincided with the beginning of intensive gait training, and  $\Delta$ PAF decreased after this training was completed. After 10 weeks, the PAF remained in the high-frequency range compared to the assessment at admission. The motor score of the ISNCSCI showed improvement, and the sensory score was perfect from the time of admission and showed no change. The 10-meter walking speed began to decrease after the start of the intervention, and the WISCI II improved, reaching the maximum score at 8 weeks. The patient was able to walk independently in the hospital at 10 weeks. The changes in each evaluation index over time are shown in Fig. 1; however, the sensory score of the ISNCSCI is not displayed because it did not change. In addition, no adverse events were observed in this intervention.

## DISCUSSION

In this case, the intensity of NP decreased over time, and the decrease coincided with the initiation of intensive gait training. The PAF began to deviate to the high-frequency range after the start of intensive gait training and then to the low-frequency range after the end of the training period; however, it remained deviated more toward the high-frequency range than that before the intervention.

The patient had been performing gait training and limb stretching according to his level of independence as self-exercises apart from the physical therapy sessions. These self-exercises continued throughout the hospital stay. In the present study, a decrease in pain intensity and a change in PAF were observed in conjunction with the start of intensive gait training, suggesting that intensive gait training significantly reduced pain.

**Table 1.** Values recorded over time.

	Time points (week)									
	Admission	2	4	6	8	10	12	14	16	18
ISNCSCI										
Motor score	88	92	95	98	99	99	99	100	100	100
Sensory score (Touch/Pin)	212/212	212/212	212/212	212/212	212/212	212/212	212/212	212/212	212/212	212/212
Pain intensity (NRS)										
Maximum	8	7.5	7	5	3	2.5	2.5	2.5	3	2
Average	7	5	5	4	3	2.5	2.5	2.5	2	2
PAF (Hz)	8.42	8.40	8.79	8.75	8.80	8.77	8.56	8.60	8.66	8.60
$\Delta$ PAF (%)	–	–0.2	4	4	5	4	2	2	3	2
10-m walk test (m/s)	–	0.62	0.93	1.24	1.52	1.76	1.76	1.75	1.96	2
WISCI II	4	8	11	19	19	20	20	20	20	20

ISNCSCI International Standards for Neurological Classification of Spinal Cord Injury, NRS numerical rating scale, PAF peak alpha frequency, WISCI II Walking Index for Spinal Cord Injury II.



**Fig. 1 The changes in each evaluation over time.** The range marked in yellow indicates the period of intensive gait training. An increase in the rate of change of PAF and a decrease in pain intensity are observed after the start of intensive gait training. Furthermore, the PAF is decreased at the end of the intensive gait training period, but it remains shifted toward a higher frequency range compared to that at the time of admission. ISNCSCI International Standards for Neurological Classification of Spinal Cord Injury, NRS numerical rating scale, PAF peak alpha frequency, WISCI II Walking Index for Spinal Cord Injury II.

Long-term intervention with gait training as an AE has been reported to decrease the intensity of NP [8–10]. We believe that the reduction in pain intensity and range observed in this case supports the findings of previous studies. One of the mechanisms by which these exercises improve NP is thought to be related to thalamocortical dysrhythmia, which can be quantitatively evaluated by calculating the PAF using resting EEG [16, 17]. In our previous study, we reported a decrease in pain intensity and a deviation of PAF toward the high-frequency range after a single session for 15 min of wheelchair propulsion in patients with SCI and NP [15]. This is likely due to sensory input from the residual area associated with the movement, which temporarily improves the dysfunction between the thalamus and cerebral cortex [19]. A systematic review of the relationship between exercise and EEG reported conflicting results for exercise-induced changes in the alpha band and could not show consistent conclusions [24]. In contrast, studies in healthy subjects have shown that high-intensity rather than low-intensity exercise resulted in a shift of PAF to higher frequencies [19, 25]. Based on the studies in which high-intensity exercise causes changes in PAF, it can be assumed that the present intensive gait training was able to cause changes in PAF because the intensity of the exercise was “somewhat hard”.

Furthermore, a study using anodic stimulation of the primary motor cortex with transcranial direct current stimulation revealed a decrease in pain and a shift of PAF around the primary motor cortex to the high-frequency range, and it has been reported that NP and PAF are closely related [26]. In the present case, PAF began to deviate to the high-frequency range with intensive gait training, followed by a reduction in pain, which is thought to be an effect of physical therapy. Additionally, the PAF shifted to the low-frequency range again after intensive gait training, suggesting that this change was related to the training. Therefore, it is suggested that physical therapy, including long-term intensive gait training, deflects the PAF into the high-frequency range and reduces pain. Notably, the patient gained the ability to walk after the end of the gait training period and was able to continue walking outside the hospital during the intervention period. Thus, the PAF was able to maintain the shift to the high-frequency range even after intensive gait training was completed, and the pain intensity continued to be reduced. Apart from these, another benefit of intensive gait training is that of analgesia. Intensive gait training can be expected to provide analgesia for upper extremity pain without direct exercise to the painful area. In the current intervention, there was a reduction in pain for 18 weeks, but no significant improvement after 14 weeks. Siddall et al. [27] reported that the prevalence of at-level NP was similar from 3 to 6 months, and that long-term improvement may not be possible. Further, they performed a 5-year follow-up and reported that the prevalence of at-level NP decreased from 3 months to 1 year, but increased for the next 5 years [28]. In the present case, the patient had high motor function early after the injury and was able to exercise from an early stage. This may have helped them to obtain the analgesic effect following exercise. We believe that it is worthwhile to continue gait training in order to maintain pain relief. However, if the injury is severe, interventions such as this one may not always be appropriate for analgesia.

The limitations of the present report include some of the natural course of the disease after cervical SCI. Second, we were not able to quantitatively assess the daytime activity of the patient. The amount of daytime activity may affect pain intensity. Likewise, it cannot be denied that pain intensity affected the amount of daytime activity throughout the intervention period.

Physical therapy, including prolonged intensive gait training as an AE in the early stage, was suggested to deflect PAF into the high-frequency range and reduce the intensity of NP. Continuous exercise may lead to improvements in the dysfunction of the thalamus-cortex neural circuit. Furthermore, PAF was closely related to pain intensity, supporting its ability to quantitatively

indicate changes in pain. In future studies, the effects of intensive gait training as an AE should be investigated in a larger number of cases.

## DATA AVAILABILITY

Original data have been stored by the corresponding author and will be made available on request.

## REFERENCES

- Levi R, Hultling C, Nash MS, Seiger A. The Stockholm spinal cord injury study: 1. Medical problems in a regional SCI population. *Paraplegia*. 1995;33:308–15. <https://doi.org/10.1038/sc.1995.70>.
- Finnerup NB, Johannesen IL, Sindrup SH, Bach FW, Jensen TS. Pain and dysesthesia in patients with spinal cord injury: a postal survey. *Spinal Cord*. 2001;39:256–62. <https://doi.org/10.1038/sj.sc.3101161>.
- Burke D, Fullen BM, Stokes D, Lennon O. Neuropathic pain prevalence following spinal cord injury: a systematic review and meta-analysis. *Eur J Pain*. 2017;21:29–44. <https://doi.org/10.1002/ejp.905>.
- Adriaansen JJE, Post MWM, de Groot S, van Asbeck FWA, Stolwijk-Swüste JM, Tepper M, et al. Secondary health conditions in persons with spinal cord injury: a longitudinal study from one to five years post-discharge. *J Rehabil Med*. 2013;45:1016–22. <https://doi.org/10.2340/16501977-1207>.
- Widerström-Noga EG, Felipe-Cuervo E, Yezierski RP. Chronic pain after spinal injury: interference with sleep and daily activities. *Arch Phys Med Rehabil*. 2001;82:1571–7. <https://doi.org/10.1053/apmr.2001.26068>.
- Ataoglu E, Tiftik T, Kara M, Tunç H, Ersöz M, Akkuş S. Effects of chronic pain on quality of life and depression in patients with spinal cord injury. *Spinal Cord*. 2013;51:23–6. <https://doi.org/10.1038/sc.2012.51>.
- Fawkes-Kirby TM, Wheeler MA, Anton HA, Miller WC, Townson AF, Weeks CAO. Clinical correlates of fatigue in spinal cord injury. *Spinal Cord*. 2008;46:21–5. <https://doi.org/10.1038/sj.sc.3102053>.
- Kressler J, Thomas CK, Field-Fote EC, Sanchez J, Widerström-Noga E, Cilien DC, et al. Understanding therapeutic benefits of overground bionic ambulation: exploratory case series in persons with chronic, complete spinal cord injury. *Arch Phys Med Rehabil*. 2014;95:1878–87. <https://doi.org/10.1016/j.apmr.2014.04.026>.
- Cruciger O, Schildhauer TA, Meindl RC, Tegenthoff M, Schwenkreis P, Citak M, et al. Impact of locomotion training with a neurologic controlled hybrid assistive limb (HAL) exoskeleton on neuropathic pain and health related quality of life (HRQoL) in chronic SCI: a case study. *Disabil Rehabil Assist Technol*. 2016;11:529–34. <https://doi.org/10.3109/17483107.2014.981875>.
- Norrbrink C, Lindberg T, Wahman K, Bjerkefors A. Effects of an exercise programme on musculoskeletal and neuropathic pain after spinal cord injury—results from a seated double-pole ergometer study. *Spinal Cord*. 2012;50:457–61. <https://doi.org/10.1038/sc.2011.160>.
- Soler MD, Kumru H, Pelayo R, Vidal J, Tormos JM, Fregni F, et al. Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury. *Brain*. 2010;133:2565–77. <https://doi.org/10.1093/brain/awq184>.
- Moseley LG. Using visual illusion to reduce at-level neuropathic pain in paraplegia. *Pain*. 2007;130:294–8. <https://doi.org/10.1016/j.pain.2007.01.007>.
- Heutink M, Post MWM, Bongers-Janssen HMM, Dijkstra CA, Snoek GJ, Spijkerman DCM, et al. The CONECISI trial: results of a randomized controlled trial of a multidisciplinary cognitive behavioral program for coping with chronic neuropathic pain after spinal cord injury. *Pain*. 2012;153:120–8. <https://doi.org/10.1016/j.pain.2011.09.029>.
- Vaegter HB, Handberg G, Graven-Nielsen T. Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans. *Pain*. 2014;155:158–67. <https://doi.org/10.1016/j.pain.2013.09.023>.
- Sato G, Osumi M, Morioka S. Effects of wheelchair propulsion on neuropathic pain and resting electroencephalography after spinal cord injury. *J Rehabil Med*. 2017;49:136–43. <https://doi.org/10.2340/16501977-2185>.
- Sarnthein J, Stern J, Aufenberg C, Rousson V, Jeanmonod D. Increased EEG power and slowed dominant frequency in patients with neurogenic pain. *Brain*. 2006;129:55–64. <https://doi.org/10.1093/brain/awh631>.
- Wydenkeller S, Maurizio S, Dietz V, Halder P. Neuropathic pain in spinal cord injury: significance of clinical and electrophysiological measures. *Eur J Neurosci*. 2009;30:91–9. <https://doi.org/10.1111/j.1460-9568.2009.06801.x>.
- Llinás RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci USA*. 1999;96:15222–7. <https://doi.org/10.1073/pnas.96.26.15222>.

19. Gutmann B, Mierau A, Hülsdünker T, Hildebrand C, Przyklenk A, Hollmann W, et al. Effects of physical exercise on individual resting state EEG alpha peak frequency. *Neural Plast.* 2015;2015:717312. <https://doi.org/10.1155/2015/717312>.
20. Bryce TN, Biering-Sørensen F, Finnerup NB, Cardenas DD, Defrin R, Lundeborg T, et al. International spinal cord injury pain classification: part I. Background and description. *March 6-7, 2009. Spinal Cord.* 2012;50:413–7.
21. Matsuki Y, Sukenaga N, Miyagi K, Tsunetoh T, Mizogami M, Shigemi K, et al. Reliability and validity of the Japanese translation of the DN4 Diagnostic Questionnaire in patients with neuropathic pain. *J Anesth.* 2018;32:403–8.
22. Klimesch W, Russegger H, Doppelmayr M, Pachinger T. A method for the calculation of induced band power: implications for the significance of brain oscillations. *Electroencephalogr Clin Neurophysiol.* 1998;108:123–30. [https://doi.org/10.1016/s0168-5597\(97\)00078-6](https://doi.org/10.1016/s0168-5597(97)00078-6).
23. Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Res Brain Res Rev.* 1999;29:169–95. [https://doi.org/10.1016/s0165-0173\(98\)00056-3](https://doi.org/10.1016/s0165-0173(98)00056-3).
24. Gramkow MH, Hasselbalch SG, Waldemar G, Frederiksen KS. Resting state EEG in exercise intervention studies: a systematic review of effects and methods. *Front Hum Neurosci.* 2020;14:155.
25. Gutmann B, Zimmer P, Hülsdünker T, Lefebvre J, Binneböbel S, Oberste M, et al. The effects of exercise intensity and post-exercise recovery time on cortical activation as revealed by EEG alpha peak frequency. *Neurosci Lett.* 2018;668:159163.
26. Ngernyam N, Jensen MP, Arayawichanon P, Auvichayapat N, Tiamkao S, Janjarasjitt S, et al. The effects of transcranial direct current stimulation in patients with neuropathic pain from spinal cord injury. *Clin Neurophysiol.* 2015;126:382–90. <https://doi.org/10.1016/j.clinph.2014.05.034>.
27. Siddall PJ, Taylor DA, McClelland JM, Rutkowski SB, Cousins MJ. Pain report and the relationship of pain to physical factors in the first 6 months following spinal cord injury. *Pain.* 1999;81:187–97.
28. Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. *Pain.* 2003;103:249–57.

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## AUTHOR CONTRIBUTIONS

GS carried out planning the work and participated in acquired the data and draft the manuscript. MO participated in the data analysis and helped to draft the manuscript. RM participated in acquire the data. SM participated in helping draft the manuscript. All authors approved the final manuscript.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ETHICAL APPROVAL

Written informed consent was obtained from the patient for the publication.

## ADDITIONAL INFORMATION

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