Educational Case Report

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Analgesic effect of paired associative stimulation in a tetraplegic patient with severe drug-resistant neuropathic pain: a case report

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Abstract

Objectives: There is no effective evidence-based non-pharmacological treatment for severe neuropathic pain after spinal cord injury (SCI). Paired associative stimulation (PAS) has been used in motor rehabilitation of patients after SCI. In the SCI-PAS protocol for tetraplegic patients, peripheral and central nerve tracts are activated with subject-specific timing, such that ascending and descending signals appear simultaneously at the cervical level. The effect on motor rehabilitation is thought to arise via strengthening of cervical upper and lower motoneuron synapses. We have observed an analgesic effect of PAS on mild-to-moderate neuropathic pain in tetraplegic patients receiving PAS for motor rehabilitation. Here, we applied PAS to a patient with severe drug-resistant neuropathic pain.

Methods: The patient is a 50-year-old man who had a traumatic cervical SCI three years earlier. He has partial paresis in the upper limbs and completely plegic lower limbs. The most severe pain is located in the right upper limb and shoulder region. The pain has not responded to either pharmacological therapy or repetitive-TMS therapy targeted to either primary motor cortex or secondary somatosensory cortex. PAS was targeted to relieve pain in the right upper arm. Peripheral nerve stimulation targeted the median, ulnar, and radial nerves and was accompanied by TMS pulses to the motor representation area of abductor pollicis brevis, abductor digiti minimi, and extensor digitorum communis muscles, respectively.

Results: Hand motor function, especially finger abduction and extension, was already enhanced during the first therapy week. Pain decreased at the end of the second therapy week. Pain was milder especially in the evenings. Numerical rating scale scores (evening) decreased 44% and patient estimation of global impression of change was 1, subjectively indicating great benefit when compared to before therapy. Quality of sleep also improved.

Conclusions: The SCI-PAS protocol reduced neuropathic pain in our subject. The mechanism behind the analgesic effect may involve the modulation of nociceptive and sensory neuronal circuits at the spinal cord level. The possibility to use PAS as an adjunct treatment in drug-resistant post-SCI neuropathic pain warrants further investigation and sham-controlled studies. Patients with neuropathic pain due to SCI may benefit from PAS therapy in addition to PAS therapy-induced improvement in motor function.

Keywords: neuropathic pain; paired associative stimulation; spinal cord injury; transcranial magnetic stimulation.

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Introduction

Paired associative stimulation (PAS) with a high-frequency peripheral component has been used in motor rehabilitation of tetraplegic patients after cervical spinal cord injury (SCI) with promising results [1–5]. In contrast to the classical PAS protocol, where long-term potentiation (LTP)-type Hebbian plasticity is produced in the cortex by repeated peripheral nerve stimulation (PNS) paired with

transcranial magnetic stimulation (TMS) [6], in SCI-PAS the time interval between PNS and TMS is adjusted such that ascending and descending neuronal volleys meet at the spinal cord level, which strengthens synapses in the damaged spinal cord. In addition, high-frequency stimulation permits effectiveness of PAS at a wider range of TMS-PNS interstimulus intervals than in conventional protocols [7, 8]. Enhanced synaptic function is thought to improve innervation in paretic limb muscles.

It is estimated that between 30 and 90% of the SCI population experiences pain [9]. Currently, there are no evidence-based non-pharmacological approaches for managing post-SCI neuropathic pain. Long-term medication is often ineffective and has side effects [9]. SCI-related pain may be divided into nociceptive pain, neuropathic pain, and other types of pain [10]. Nociceptive pain includes musculoskeletal and visceral pain. Musculoskeletal pain is the most common pain type with a prevalence of approximately 60% in SCI patients [11]. Neuropathic pain associated with SCI may be divided into at-level and below-level pain, based on the dermatomal distribution of pain in relation to the damaged nerve root and spinal cord levels. According to a meta-analysis, the prevalence of neuropathic pain is approximately 53% in SCI patients [12]. Post-SCI neuropathic pain is often severe and difficult to treat. In general, neuropathic pain may arise from the periphery, spinal cord, brain, or combinations thereof. At the spinal cord level, several mechanisms may contribute to pain. Previous studies have shown that the firing thresholds of dorsal horn neurons close to the damaged area are increased. This increased firing is related to altered levels of neurotransmitters and receptors that may increase excitation or reduce inhibition. SCI also causes glial activation and release of proinflammatory cytokines and prostaglandins, which may contribute to pain [10, 13, 14]. Structural reorganization of afferent nerve fibers also occurs in the spinal cord. In addition, descending antinociceptive pathways may be damaged and this may also correlate with pain intensity [10, 15].

Our earlier SCI-PAS studies directed at motor rehabilitation [1–4, 16, 17] had a total of seven patients with mild-to-moderate neuropathic pain; six of these patients experienced decreased pain (results reported in these previous publications, see Table 1 for results summary). This encouraged us to test the SCI-PAS protocol for a patient with severe drug-resistant at-level neuropathic pain in the right upper limb and shoulder region. Our hypothesis was that the SCI-PAS protocol could be used to drive an altered excitation/inhibition equilibrium in the spinal cord dorsal horn fibers towards a more normal state, resulting in decreased SCI-related neuropathic pain.

Case description and methods

SCI PAS therapy was performed in the BioMag Laboratory in Helsinki University Hospital. Therapy was performed in accordance with the Helsinki Declaration and was approved by the Ethics committee of Helsinki University Hospital. The experimental nature of the therapy was explained to the patient and the patient provided his written permission for publication of the results. Our patient is a middle-aged male with a long history of depression and partial cervical SCI and tetraparesis due to C6–C7 traumatic vertebral fractures and luxation since December 2015. After cervical trauma, emergency surgery was performed acutely. Two months after trauma, control magnetic resonance imaging (MRI) showed failed fixation and luxation and re-operation was performed. Before re-operation, tetraparesis was partial in the upper limbs while lower limbs were plegic. Sensory dysfunction was located below C5/C6 level and motor dysfunction below C6/C7 level. The patient reported neck pain and pain in both upper limbs soon after trauma. After reoperation, the pain was located mainly on the right and was most intense in the shoulder and scapulae region and somewhat milder in the ribs and in right upper limb. The level for cold perception was situated in the scapulae region above the area with the most intense pain. In addition to pain, dynamic allodynia was observed in C8 dermatome from shoulder to fingers. Sharp and blunt touch perception was normal in the upper and lower back region. Muscle stiffness was observed in the right paraspinal region near the scapulae and in the muscles above the scapulae. Right shoulder MRI showed partial rupture in the supraspinatus tendon, fraying in the tendon of the long head of biceps brachii muscle, and mild degenerative findings in the shoulder without severe muscular fat atrophy. Electroneuromyography showed severe right-sided C8 nerve root damage in July 2016. Pain was interpreted to include central and peripheral neuropathic and nociceptive components. The neuropathic component of pain was thought to arise from both the spinal cord and nerve root. The nociceptive component arose from the glenohumeral joint and muscle stiffness. A broad range of analgesic medications was tested, including pregabalin, lamotrigine, amitriptyline-chlordiazepoxide, duloxetine, strong opioids (methadone and oral oxycodone/naloxone combination), non-steroidal anti-inflammatory drugs (NSAIDs), and muscle relaxants. Sleep-inducing drugs were used for sleeping problems. The last visit to a psychologist was 4 years earlier. At that time, the psychologist believed that the patient would benefit from regular meetings but the patient was not motivated to continue. Despite multiple medications and

Table 1: Summary of pain-related observations in studies on SCI-PAS with high-frequency peripheral stimulation for chronic spinal cord injury patients. Only studies which included patients with neuropathic pain are presented.

Article, duration of paired associative stimulation (PAS)	Peripheral nerve stimulation (PNS) frequency	Total number of patients/patients with neuropathic pain/patients whose pain diminished	Results
Shulga et al. [2, 7], 20–24 weeks	50 Hz	2/2/2	Before PAS, patient a reported almost daily throbbing bilateral pain in close proximity to the L2 sensory level. The level of pain was 3–6 on the visual analog scale (VAS; 0-no pain; 10-worst possible pain). During the first week after PAS, the pain diminished bilaterally, although only the left leg/right cerebral hemisphere was stimulated. During the six-month experiment, the patient experienced pain (VAS 4–5) only on 11 days (half of these 11 days were associated with an infection). During the 2 weeks without PAS due to the patient's vacation, the pain did not return. During the follow-up period (one month), the patient experienced pain (VAS 5) over 4 days; the pain was associated only with provoking stimuli. Before the experiment, patient B reported pain of VAS 7 in the right shoulder and scapular area about 3 times per week. After 10 PAS sessions, the pain occurred approximately once in 2 weeks (VAS 7) and only in the shoulder area. During the follow-up period (1 month), the incidence and area of pain did not increase.
Tolmacheva et al. [1], 4 weeks	50 Hz	5/2/1	Patient 1 reported constant unpleasant tingling in both arms and feet; the tingling was absent after the intervention. Patient 5 reported bilateral occasional pain between the elbows and wrists (1 h daily, VAS 3) before the intervention. After the intervention, she experienced approximately similar pain (1 h daily, VAS 4–5). This increase was probably due to interruption of local peripheral stimulation to the wrists. After the follow-up period, the local peripheral stimulation was resumed and the pain intensity returned to VAS 3.
Rodionov et al. [4], 47 weeks	50–100 Hz	1/1/1	The patient experienced continuous neuropathic hand pain (VAS 2) and tingling and burning sensations on the lateral surfaces of both arms and forearms before the intervention; pain and abnormal sensations gradually disappeared during first months of stimulation and was not present after the intervention or during the 4-month follow-up period. The patient also had cold allodynia in both hands before intervention; this gradually disappeared from the left hand during the first months of stimulation and was absent in the left hand after the intervention and during the follow up. Neuropathic pain in the legs remained unchanged (only hands were stimulated).
Rodionov et al. [17], 8 weeks	100 Hz	5/1/1	Participant 5 reported that pain disappeared in the right ankle after PAS.

Table 1: (continued)

Article, duration of paired associative stimulation (PAS)	Peripheral nerve stimulation (PNS) frequency	Total number of patients/patients with neuropathic pain/patients whose pain diminished	Results
Shulga et al. [16], 12 + 12 weeks	100 Hz	1/1/1	Before the first PAS intervention, the patient had unpleasant tingling in both legs (entire leg area) for about 5 h per day; these sensations disappeared after the intervention. Before the second PAS intervention (9 months after discontinuation of the first intervention), he experienced continuous tingling and unpleasant sensations (VAS 3–4) in both legs starting from the mid-thighs and extending distally; in addition, he had pain in the lower abdomen. After the second PAS intervention, pain in lower abdomen diminished but there were no other changes in pain.

VAS, visual analog scale, NA, not applicable. As pain was not the primary outcome variable in these studies, some of the studies lack precise information on pain levels in different phases during and after therapy. In all studies, TMS was given at 100% of maximum stimulator output and PNS at either 50 or 100 Hz (values indicated in the table). In all studies, PAS was given 5 times per week during first 2 weeks, and 3 times per week thereafter.

physiotherapy, pain was intense and remained at a level of 5–10/10. Transcutaneus electrical nerve stimulation (TENS) was also tested and produced a very short-lasting effect (a few days at the beginning of the treatment) but without sustained and repeated benefit. A spinal cord stimulator was not recommended due to the excessively narrow epidural space. Repetitive transcranial magnetic stimulation (rTMS) therapy was performed in January 2019 without any pain relief. The targets for high-frequency (10 Hz, 10-s trains, 20-s inter-train intervals, total of 3030 pulses, pulse intensity 90% of resting motor threshold of distal hand muscle) rTMS stimulation were the primary motor cortex (right hand representation area) in the left hemisphere and followed by the secondary somatosensory cortex in the left hemisphere, which have both been used as target areas in rTMS pain therapy [18–20].

We decided to test SCI PAS therapy, as patients using this therapy reported pain reduction and improvements in motor function (Table 1). Therapy was performed 3–4 days/week over four weeks.

Determination of the interstimulus interval (ISI) between peripheral nerve stimulation and cortical TMS stimulation was performed as previously described [21]. First, F-wave latencies were measured separately for median, ulnar, and radial nerves with a Dantec Keypoint device (Natus Medical Inc., Pleasanton, CA, USA). Two stimulating surface electrodes were placed over the skin above the median and ulnar nerves in the wrist and above the radial nerve in the upper arm. Compound muscle action potentials (M- and F-waves) were recorded from the abductor pollicis brevis (APB), abductor digiti minimi (ADM), and extensor digitorum communis (EDC) muscles. TMS was then targeted to the motor representation areas of these muscles in the left primary motor cortex. Latencies for motor-evoked potentials (MEPs) were determined based on approximately 10 stimulations with suprathreshold stimulation intensity (120% of resting motor threshold) per representation area. The motor threshold for APB was 40%, for ADM 50%, and for EDC 40% of maximum stimulator output. ISI was calculated with the formula F-wave latency minus MEP latency. The difference was positive, meaning that PNS preceded TMS pulse [21]. The magnitude of the current in PNS was determined based on the minimum current eliciting F-waves as previously described [1]. SCI-PAS therapy was conducted according to previous studies [1, 3], with 240 repetitions of PNS-TMS pulse pairs per nerve with an intertrial interval of 5 s. PNS was delivered as 100-Hz trains of 6 1-ms pulses. The total duration of the treatment was 20 min per nerve and 60 min per daily session. The therapy was performed over 4 weeks, 4 days per week in the first 2 weeks and 3 days per week in the last 2 weeks. In the last 2 weeks, daily stimulation sessions were performed in three consecutive days, which differed slightly from the classical SCI-PAS protocol in which stimulations are performed every other day during the week (resulting in 3 therapy days per week) and where PAS is administered 5 days per week during the first 2 weeks.

Subjective pain intensity and pain disturbance of sleep were followed daily for 2 weeks before the treatment period, during the 4-week treatment period, and 40 days after treatment. A numerical rating scale (NRS) of 0–10 was used to describe pain intensity and disturbance of sleep,

where 0 indicates no pain or no disturbance of sleep at all and 10 the most severe pain or the most severe disturbance of sleep that one can imagine. Patient global impression of change (GIC) was assessed after the treatment period. The GIC scale ranges between 1 and 7, where one indicates that patient benefited a lot and seven indicates that overall situation is considerably worse than before treatment. The patient was asked to estimate his own expectation of the benefit of the therapy. Patient was asked to select from five options on how much he expected the rTMS therapy to decrease pain. Those five options were not at all, less than half, about half, more than half, and completely. Depression or anxiety was not estimated before treatment. Analgesic medication was not modified during the 4-week treatment period. However, 3 weeks before therapy, olanzapine was added as medication for pain and insomnia. During therapy, the medication was pregabalin 300 mg × 2, lamotrigine 200 mg × 2, duloxetine 90 mg × 1, olanzapine 10 mg × 1, amitriptyline hydrochloride 14.15 mg/chlordiazepoxide 5 mg 2 × 1, zopiclone 7.5 mg × 1 for insomnia, and tizanidine hydrochloride 6 mg 1 × 2 for spasticity daily.

Motor function tests were conducted by an experienced physiotherapist before treatment, 1 week after the end of treatment, and at the end of the 40-day follow-up period. The evaluation included: (1) manual muscle test (MMT), which is used to measure strength in the upper limbs, (2) Spinal Cord Independence Measure (SCIM) to estimate self-care, respiration, sphincter management, and patient mobility, (3) Modified Ashworth Scale (MAS), which measures spasticity, and (4) AIS examination to determine the motor and sensory function at different myotome and dermatome levels.

Results

Pain

At baseline, pain intensity was 6–8.5 in the right upper arm and shoulder region in the mornings (mean 7) and 7–10 in the evenings (mean 8) (Figure 1A). Pain disturbance of sleep varied between 3 and 8 (mean 4). The patient expected that the pain would decrease by about half due to therapy.

Pain registered in the evenings decreased at the end of the second therapy week (Figure 1B). At the end of the third therapy week, pain was less intense also in the mornings. During the fourth and final therapy week, NRS values varied between 4 and 6 (mean 5) in the mornings and between 2 and 8 (mean 5) in the evenings. When NRS scores were compared between the last therapy week and baseline, mean morning scores decreased 29% and mean evening scores 41%. Sleep disturbance scores decreased from 4 (mean in baseline) to 2 (mean in last treatment week). The patient estimated GIC as one, meaning that he experienced great benefit from the treatment. In verbal comments at the end of the treatment, he reported that the most significant benefit was pain relief and better sleep quality, yielding a more vivacious state of being. After that he mentioned better motor function of the right hand. The patient did not report any side-effects.

The follow-up period lasted 40 days after the treatment. Pain intensity increased approximately 1.5 weeks after the end of the treatment towards baseline level. NRS morning values varied during follow-up period between 5 and 8 (mean 7) and evening values between 5 and 10 (mean 7) (Figure 1C).

Hand motor function

Consistent with our previous results, the patient reported enhanced motor function in the right hand already after the first therapy week. MMT showed increased force in the right upper limb in the ulnar and radial nerve-innervated muscles in the first evaluation 1 week after the therapy period (Figure 2A). In the second evaluation after the 40-day follow-up period, increased force was observed in the right upper limb in the radial, median, and ulnar nerve-innervated muscles; the further increase in muscle strength in the follow-up is also consistent with our previous studies. In the left (unstimulated) upper limb, force was initially increased in the radial nerve-innervated muscles and decreased in median nerve-innervated muscles in the first control, but values reverted back to baseline after follow-up (Figure 2B). AIS light touch sensory testing showed a 1-point decrease in the left C5 myotome in the second control. Other tests did not show any changes between baseline and control measurements after treatment (Table 2).

Discussion

We present a case report where a SCI patient with severe refractory pain had transient pain reduction after PAS treatment. We also briefly summarized our previous experiences with long-term PAS on mild-to-moderate neuropathic pain (Table 1) in SCI patients.

After SCI, extensive and often maladaptive remodeling occurs in the ascending and descending tracts and in local

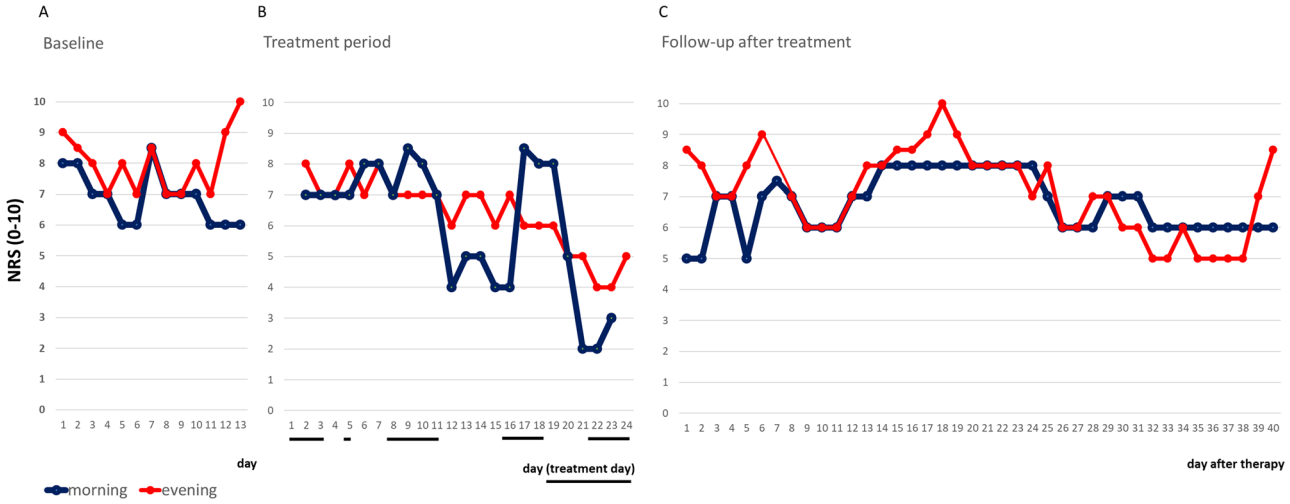

Figure 1: Pain on numerical rating scale (NRS) scale. (A) Pain intensity for the two weeks (13 days) before rTMS treatment estimated by the patient on NRS (0–10). In NRS, 0 means no pain at all and 10 the most intense pain that one can imagine. (B) Pain intensity during the treatment period. Treatment days are shown in the x-axis. Pain intensity decreased at the end of the second treatment week (11 days after beginning of treatment). According to the patient, the peak in evening values in days 17–19 appeared after a taxi ride, which caused body shaking. (C) Pain intensity in the 40-day follow-up period after treatment. One evening value was not marked (day 7). The diagram shows that treatment effect on pain was brief and after two weeks NRS scores were at the same level as baseline.

interneurons of the spinal cord. Due to deprivation of normal input activity, the balance between excitation and inhibition is distorted, and new inappropriate connections are born through sprouting, leading to spasticity and pain [22]. Strengthening the appropriate pathways with neuromodulation might drive the balance in the system towards a more normal state and reduce pain. Indeed, in our previous reports where SCI patients had milder pain than the patient reported here, the reduced pain persisted at least until the end of the follow-up periods of 1–4 months (Table 1). Consistent with our previous studies, the force in the paretic right upper limb of the patient reported here increased after PAS, and the effect on the motor system also persisted after follow up. Pain decreased during the therapy significantly and the patient considered that the overall situation was much better than at baseline. However, the effect of SCI-PAS on pain gradually disappeared during the follow-up period. This might indicate that better function of the corticospinal pathway is likely not solely responsible for the therapeutic effect in this particular case.

As this pilot study did not include sham stimulation, the placebo effect cannot be excluded. rTMS has a significant placebo effect in the treatment of mental disorders and pain [23, 24]. A possible placebo effect must also be considered in this case study, although it was previously reported that preceding unsuccessful rTMS treatments reduce the probability of placebo effect in subsequent TMS treatments [24].

It is noteworthy that this patient did not previously respond to rTMS treatment (see Introduction). PAS consists of 0.2-Hz TMS pulses given at 100% and PNS trains given at the intensity required to produce an F-response (to ensure that the stimulation reaches the spinal cord). As previously discussed [1, 5, 16, 25], the effect on the motor system is due to the dual stimulation. However, regarding the effect on pain, further sham-controlled studies are required to elucidate whether TMS, PNS, or the dual stimulation are responsible for the therapeutic effect. When rTMS alone is used, lasting inhibitory aftereffects can be achieved with 1-Hz repetitive TMS and facilitatory aftereffects with high-frequency (HF) (>5 Hz) repetitive TMS [26]. In healthy subjects, TMS given at 0.2-Hz frequency and PNS component alone do not increase MEPs and thus do not induce plastic changes on their own [2, 8]. Peripheral electrical stimulation is used to elicit competing sensory input in pain patients and could also explain the analgesic effect. TENS is not known to produce a long-term effect beyond the actual stimulation period and thus requires continuous application [27]. Our patient had benefited from TENS treatment earlier only for a few days, while in SCI-PAS therapy the effect was observed in between the stimulation days (Figure 1) and for about 1 week after the stimulation session. Interestingly, in our recent study where we applied a stimulation protocol similar to PAS but without the TMS component (i.e. we provided only PNS combined to motor imagery) on five tetraplegic patients, none of the patients with neuropathic pain (three patients total) reported pain

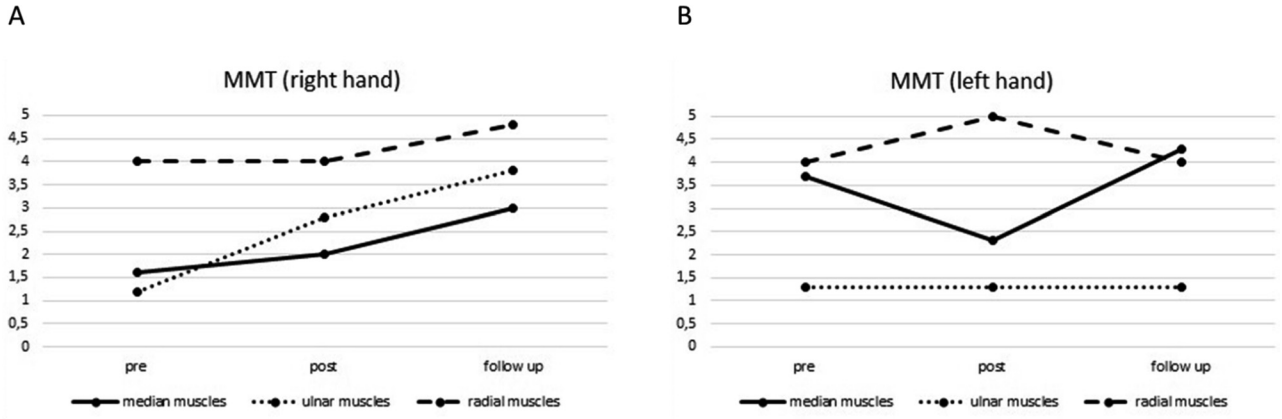

Figure 2: Manual muscle test (MMT) scores before and after treatment and after the follow-up period in (A) right and (B) left hands.

Table 2: Summary of motor and sensory function tests before and after treatment and after follow up.

	Baseline right/left (mean)	After treatment right/left (mean)	After follow up right/left (mean)
MMT	2.14/2.71	2.86/2.29	3.79/3.0
SCIM	17	17	17
MAS	0	0	0
AIS motor C5, C6, C7, C8	5/5	5/5	5/5
AIS motor T1	3/0	4/1	5/5
AIS sensory light touch (C2-Th1)	18/17	18/17	18/16
AIS sensory pin prick (C2-Th1)	18/18	18/18	18/18

AIS, ASIA impairment scale; MAS, modified Ashworth Scale; MMT, manual muscle test; SCIM, spinal cord independence measure. In MMT mean scores, only scores from those muscles in which the baseline level was <5 are included.

reduction [25]. In the patient reported here, the effect on pain only appeared two weeks after initiation of PAS and not immediately. Taken together, it is possible that the analgesic effect is due to plastic changes specifically related to dual stimulation.

Olanzapine [28] was added three weeks before therapy. However, the therapeutic effect was observed only 2 weeks after PAS initiation (i.e. five weeks after olanzapine initiation), thus making this drug an unlikely cause of the effect. The increase in pain intensity toward previous levels upon discontinuation of PAS (during ongoing olanzapine therapy) also indicates that PAS was responsible for the effect.

It is possible that a longer stimulation period would have been required for more durable pain relief. Furthermore, although time-consuming, even maintenance treatment with PAS given e.g. 2–3 days per week might be an option for patients who suffer from drug-resistant pain and for whom other forms of neuromodulation (such as rTMS or electrical spinal cord or nerve root stimulation) are ineffective or contraindicated. Patients with pain are usually well motivated to visit the hospital even several days per week for effective pain relief. Our subject would have also been motivated to continue the treatment if possible. Further research is needed to determine the optimal management strategies for severe refractory neuropathic pain after SCI.

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Informed consent: Informed consent has been provided by the patient described in this case report.
Ethical approval: The research related to human use complies with all the relevant national regulations and institutional policies and was performed in accordance with the tenets of the Helsinki Declaration and has been approved by the Ethics committee of Helsinki University Hospital.

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