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Motor cortex stimulation in the treatment of neuropathic pain

Stymulacja kory ruchowej w leczeniu bólów neuropatycznych

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Abstract

Background and purpose: Despite the rapid development of neuropharmacotherapy, medical treatment of neuropathic pain (NP) still constitutes a significant socioeconomic problem. The authors herein present a group of patients treated with motor cortex stimulation (MCS) for NP of various types and aetiologies.

Material and methods: Our cohort included 12 female and 11 male NP patients aged 53 ± 16 treated with MCS. Eleven patients were diagnosed with neuropathic facial pain (NFP), 8 with hemi-body neuropathic pain (HNP), and 4 with deafferentation pain (DP). Prior to surgery, 16 out of 23 patients were treated with repetitive transcranial magnetic stimulation (rTMS), with a positive response in 10 cases. Pain intensity in our group was evaluated with the visual analogue scale (VAS) one month before and three months after MCS implantation.

Results: Improvement on the VAS was reported in the whole group of patients ($p < 0.001$). The best results were reported in the NFP group ($p < 0.001$) while the worst ones were noted in the DP group ($p = 0.04$). Anamnesis duration positively correlated with outcome. Infection forced the authors to permanently remove the system in one case. There were no other complications in the group.

Streszczenie

Wstęp i cel pracy: Pomimo dynamicznego rozwoju neurofarmakoterapii, leczenie bólów neuropatycznych stanowi istotny problem socjoekonomiczny. Autorzy przedstawiają grupę chorych leczonych metodą stymulacji kory ruchowej (*motor cortex stimulation* – MCS) z powodu bólów neuropatycznych o różnym obrazie klinicznym i etiologii.

Materiał i metody: W grupie 12 kobiet oraz 11 mężczyzn w wieku 53 ± 16 lat zastosowano MCS z powodu bólu neuropatycznego. U 11 chorych rozpoznano neuropatyczne bóle twarzy, u 8 chorych połowiczy ból neuropatyczny, a u 4 chorych – ból deaferentacyjny. U 16 chorych przeprowadzono próbną przezczaszkową stymulację magnetyczną, uzyskując przejściową poprawę u 10 z nich. Nasilenie dolegliwości bólowych oceniano z wykorzystaniem wzrokowej skali analogowej (*visual analogue scale* – VAS) miesiąc przed implantacją oraz w trzecim miesiącu po implantacji MCS.

Wyniki: U wszystkich chorych w grupie stwierdzono poprawę mierzoną VAS ($p < 0{,}001$). Najlepsze efekty leczenia bólu neuropatycznego zaobserwowano w grupie chorych z neuropatycznym bólem twarzy ($p < 0{,}001$), a najsłabsze u chorych z rozpoznanym bólem deaferentacyjnym ($p = 0{,}04$). Długość wywiadów korelowała dodatnio z wynikami leczenia. U jednego chorego ze względu na zakażenie usunięto system

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Conclusions: Minimally invasive, safe neuromodulative treatment with MCS permits neuropathic pain control with good efficacy. The type of neuropathic pain might be a prognostic factor.

Key words: neuropathic pain, cortical stimulation, transcranial magnetic stimulation.

i nie podejmowano próby ponownego wszczepienia. Innych powikłań w grupie nie stwierdzano.
Wnioski: Wykorzystanie minimalnie inwazyjnych technik neuromodulacyjnych, w tym MCS, pozwala na skuteczne i bezpieczne zmniejszenie nasilenia bólów neuropatycznych. Rodzaj bólu neuropatycznego może mieć znaczenie rokownicze.

Słowa kluczowe: bóle neuropatyczne, stymulacja kory ruchowej, przezczaszkowa stymulacja magnetyczna.

Introduction

The 'decade of the brain' without any doubts positively influenced the development of neuropharmacotherapy. Unfortunately, the efficacy of neuropathic pain treatment, regardless of contemporary, conservative treatment modalities, is unsatisfactory for a significant percentage of patients. Neuropathic pain arises from peripheral, central or sympathetic nervous system injury. It has been estimated that neuropathic pain affects 3% of the general population while being the leading cause of disability for as many as 30% of cancer patients and an additional 10% of patients following radio- and/or chemotherapy. Neuropathic pain is usually constant, burning and often with related dysaesthesia. Mechanic or thermal allodynia is usually present with concomitant hypoaesthesia or anaesthesia. Patients describe neuropathic pain as a sensation of burning, stinging or pulling, sometimes even like a viper bite. A significant number of patients have a considerable autonomic component of neuropathic pain. Neuropathic pain might have focal character, encompassing single dermatomes (e.g. peripheral neuropathic pain, phantom pain), or might cover large regions (e.g. thalamic pain) [1-3]. Its pathophysiology is unclear. Melzack and Wall in 1965 proposed a control gate theory that only partially explains the mechanism of neuropathic pain. Accordingly, a disinhibition of afferent nociceptive impulsation at the level of posterior horns of the spinal cord, brainstem or midbrain results in a constant perception of pain in the given body region.

The history of neuromodulation implementation in the treatment of neuropathic pain reaches back to the 1950s. The attempts to instigate ablative techniques, similarly to the deep brain structures, in the treatment of neuropathic pain furnished unsatisfactory results. Conversely, deep brain stimulation results in an improvement in a selected group of neuropathic pain patients, but still the implantation procedure, especially when compared to motor cortex stimulation (MCS), is burdened by a high risk of complications. Moreover, side effects that often coexist with a favourable analgesic effect significantly diminished its popularity. The introduction of cortical stimulators raised hope for a quality of life improvement for patients with NP. The attempts of sensory cortex stimulation rendered little if any of the expected results, often worsening the symptoms. The introduction of MCS by Meyerson and Tsubokawa in 1991 and 1993, however, resulted in significant amelioration of symptoms for the majority of patients [4-10].

The mechanism of MCS action is not known, and the role of activation of the thalamus, cingulate gyrus, fronto-orbital cortex, brainstem and periaqueductal gray matter present in positron emission tomography during stimulation is unclear [8]. Fifteen years after the introduction of MCS, the efficacy of neuropathic pain treatment with this modality still increases while the necessity for trial external stimulation that lasts for weeks diminished over the years owing to the introduction of neuronavigation, elaboration of proper functional magnetic resonance imaging (fMRI) protocols and implementation of intraoperative somatosensory and motor evoked potentials [11-13].

The authors present a group of patients with diagnosed neuropathic pain of various aetiologies treated with MCS. The aim of the study is to evaluate the efficacy and safety of MCS in neuropathic pain.

Material and methods

Twelve women and 11 men with neuropathic pain aged 53 ± 16 years were implanted with MCS devices. Anamnesis in our group varied from 2 to 32 years (mean 12 years).

Eleven patients (9 women and 2 men) were diagnosed with neuropathic facial pain (NFP). In 3 patients, NFP followed thalamic stroke, in 4 cases it resulted from craniofacial surgery (posttraumatic in 3 patients

and related to benign neoplasm in 1 patient) and in 4 patients it occurred as a complication of ablative treatment for trigeminal neuralgia. Eight patients underwent transcranial magnetic stimulation (rTMS) that resulted in pain reduction in 6 patients. Pain intensity was assessed with the visual analogue scale (VAS) and averaged 8 (7-9.5).

Hemi-body neuropathic pain (HNP) was diagnosed in 8 patients (6 men and 2 women), including 5 patients with thalamic stroke and 3 patients with spinal cord injury. All of the patients underwent rTMS that resulted in pain reduction in 4 patients. Pain intensity was evaluated with the VAS scale with average intensity of 8.5 (7-9.5).

Four patients (3 men and 1 woman) presented with deafferentation pain (DP) of the upper extremity following avulsion injury of the brachial plexus. No rTMS was implemented. Again, pain intensity was evaluated with the VAS scale with average intensity of 8 (7.5-9.5).

In 16 patients in our cohort, trial rTMS was performed that resulted in transient improvement in 10 patients, which was recognized as a positive prognostic factor.

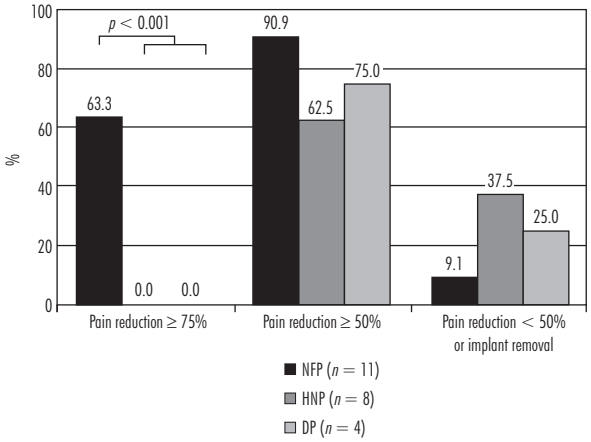
Prior to surgery, MRI was performed in all of the patients. Based on imaging studies cortical structures in axial, sagittal and coronal planes were identified. Functional MRI was simultaneously performed in order to identify the regions of the motor cortex relevant for the salient pain.

Surgery was performed under general anaesthesia following preoperative planning with a neuronavigation system that allowed identification of the region of the motor cortex relevant for the given pain type. Frontoparietal craniotomy was followed by implantation of electrodes (either two four-contact electrodes or one eight-contact electrode). Intraoperative somatosensory and motor evoked potentials were assessed in 16 patients in order to confirm electrodes' localization. Then the system was internalized and electrodes were fixed to the dura. A stimulating electrode was subsequently connected to the stimulator with an interconnecting electrode and a whole system was internalized (Itrel 3 or Synergy, Medtronic). Stimulation amplitude was then increased over the first 24 hours after surgery and aimed at subthreshold values for the motor response of 20-50 Hz frequency, 60-200 ms impulse width and stimulation times of 30-120 minutes in 1-6 cycles per 24 hours.

Pain intensity was evaluated with the VAS scale a month prior to and 3 months after initiation of stimulation.

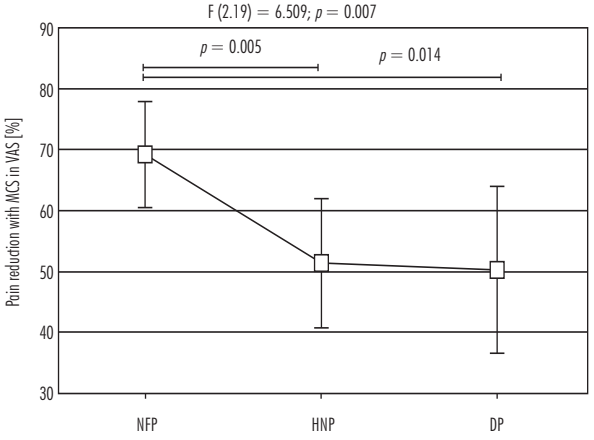
Statistical analysis

Nominal or ordinal scale variables are presented as percentages with 95% confidence interval (95% CI). Continuous variables with normal or close to normal distribution are presented as the arithmetic mean with 95% CI. For continuous variables with distribution significantly different from normal, we used either median or mean with range. Distribution plots represent single observations along with linear regression with 95% CI. The size of a given data point expresses the number of observations in a given arrangement of values (large point for 2 and very large point for 3 identical observations).



NFP – neuropathic facial pain; HNP – hemi-body neuropathic pain; DP – deafferentation pain

Fig. 1. Efficacy of the treatment measured as pain reduction (visual analogue scale) depending on the type of neuropathic pain



NFP – neuropathic facial pain; HNP – hemi-body neuropathic pain; DP – deafferentation pain VAS – visual analogue scale

Fig. 2. Efficacy of motor cortex stimulation (MCS) in relation to the type of pain

Comparative analysis of qualitative variables was performed with the χ^2 test. For expected numbers < 5, two-tailed Fisher exact test was then used. Comparisons of quantitative variables were performed with Mann-Whitney *U*-test for independent variables or Wilcoxon rank test for dependent variables. Analysis of variance (ANOVA) was implemented for comparisons of higher numbers of independent variables.

For selected sets of quantitative variables, linear regression and Pearson correlation coefficients were calculated. Linear regression equations are presented only for statistically significant correlations. Single, outlying data points were excluded from the analysis based on visual evaluation of distribution plots and the influence of a given outlying data point on linear regression slopes.

All statistical analyses were performed with STATISTICA 8.0 (StatSoft, Inc. 2008) software with the significance level set at $p < 0.05$ for all the tests.

Table 1. Cumulative characteristics of the motor cortex stimulation (MCS) group

Age [years]	53.1 (47.1-59.2)
Males	47.8% (29.2-67.0)
Pain type	
Neuropathic facial pain*	47.8% (29.2-67.0)
Hemi-body neuropathic pain*	34.8% (18.8-55.1)
Deafferentation pain*	17.4% (7.0-37.1)
Transcranial magnetic stimulation responders ($n = 16$)	62.5% (38.6-81.5)
Pain intensity prior to MCS [VAS]	8.3 (8.0-8.6)
Pain intensity with MCS [VAS]	3.4 (2.8-4.0)
Improvement after MCS [% VAS]†	59.3% (52.8-65.7)
Improvement ≥ 50%*	81.8% (61.5-92.7)
Improvement ≥ 75%*	31.8% (16.4-52.7)

CI – confidence interval; VAS – visual analogue scale
Data are presented as means (95% CI) or, when marked with an asterisk, as ratio (95% CI).
**Case of explantation was counted as treatment failure.*
†Calculated as (MCS OFF – MCS ON)/MCS OFF

Results

All of the patients in our cohort showed significant improvement when assessed with the VAS ($p < 0.001$). The best outcome was found in patients diagnosed with NFP ($p < 0.001$). Worse results were achieved in patients treated with MCS for HNP ($p < 0.001$) or for DP ($p = 0.04$) (Figs. 1 and 2, Tables 1 and 2).

Ten patients with NFP (90.9%; 95% CI: 62.3-98.4%) showed at least a good response to stimulation, i.e. ≥ 50% reduction of pain during follow-up. Percentage of improvement was assessed based on VAS scale scores prior to and three months after surgery. A very good response (pain reduction by at least 75%) was achieved in 7 patients (64%; 95% CI: 35.4-84.5%). Treatment was unsuccessful in one patient (9%; 95% CI: 1.6-37.7%; Fig. 3).

Table 2. Comparative characteristics of the group based on the type of pain

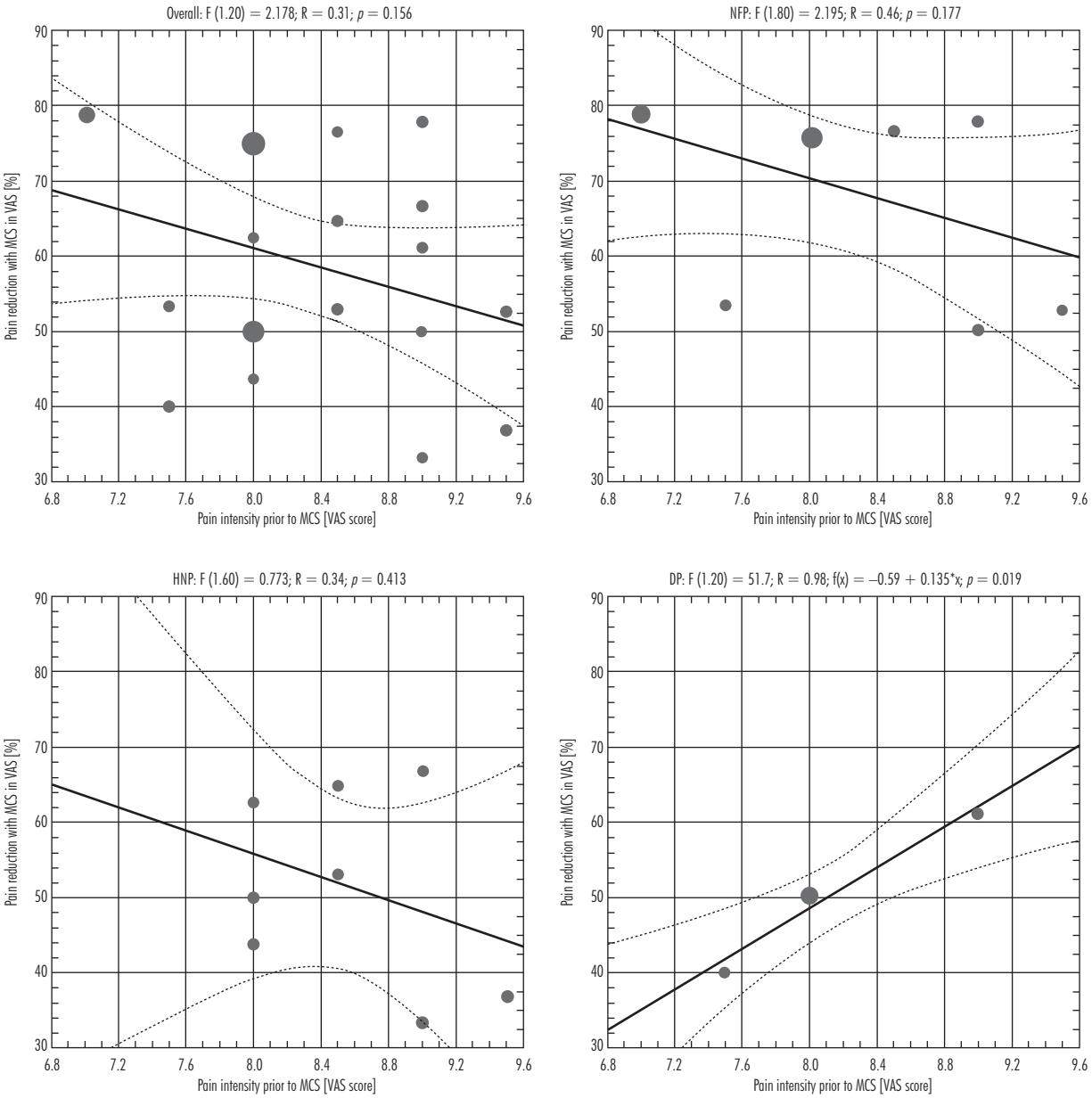
	Neuropathic facial pain ($n = 11$)*	**Hemi-body neuropathic pain ($n = 8$)**	**Deafferentation pain ($n = 4$)**	***P*-value**
Age [years]	58.4 (51.1-65.6)	48.9 (35.7-62.0)	47.3 (21.0-73.5)	0.232
Males†	18.2% (5.1-47.7)	75.0% (40.9-92.9)	75.0% (30.1-95.4)	0.024
Transcranial magnetic stimulation responders ($n = 16$)	62.5% (30.6-86.3)	62.5% (30.6-86.3)	Not done	1.000
Pain intensity prior to MCS [VAS]	8.1 (7.6-8.7)	8.6 (8.1-9.0)	8.1 (7.1-7.1)	0.398
Pain intensity with MCS [VAS]	2.6 (1.7-3.4)	4.2 (3.1-5.2)	4.0 (3.4-4.6)	0.013
Improvement after MCS [%VAS]‡	69.2% (60.6-77.8)	51.3% (40.7-62.0)	50.3% (36.6-64.0)	0.007
Improvement ≥ 50%†	90.9% (62.3-98.4)	62.5% (30.6-86.3)	75.0% (30.1-95.4)	0.113
Improvement ≥ 75%†	63.6% (35.4-84.8)	0% (0.0-32.4)	0% (0.0-49.0)	0.002

MCS – motor cortex stimulation; CI – confidence interval; VAS – visual analogue scale
Data are presented as means (95% CI) or, when marked with†, as ratio (95% CI).
**Case of explantation was counted as treatment failure.*
‡Calculated as (MCS OFF – MCS ON)/MCS OFF

In the HNP group, at least a good response to stimulation was achieved in 6 patients (75%; 95% CI: 40.9-92.9%). None of the patients showed a very good response (95% CI: 0.0-32.4%). Pain reduction by less than 50% was achieved in 2 patients with spinal cord injury (25%; 95% CI: 7.1-59.1%; Fig. 3).

All patients with DP of the upper extremity reported pain reduction. Three of them (75%; 95% CI: 30.1-95.4%) had a good response to the treatment. None of the patients showed a very good response (95% CI: 0.0-49.0%). Pain reduction by less than 50% was achieved in one patient (25%; 95% CI: 4.6-69.9%, Fig. 3).

The severity of pain assessed with the VAS scale was comparable between the groups prior to implantation. Stimulation resulted in a statistically significant reduction of pain intensity in all of the groups. The best res-



NFP – neuropathic facial pain; HNP – hemi-body neuropathic pain; DP – deafferentation pain; VAS – visual analogue scale

Fig. 3. Linear regression of the dependency between pain intensity and efficacy of motor cortex stimulation (MCS) treatment in each pain type

ponse ($p < 0.05$) was achieved in patients with NFP. In the whole group, as well as in NFP and HNP groups, we found no relationship between initial pain intensity and the outcome of treatment. Nonetheless, linear regression analysis revealed a very strong and statistically significant positive correlation in the DP subgroup (Table 2).

A good response to rTMS was found in 10 patients. Six patients did not show any reduction of the pain intensity. A statistically significant ($p = 0.036$) difference was present in the MCS group following rTMS in the frequency of at least a good response to treatment for all (95% CI: 72.2-100%) and for 3 patients (95% CI: 18.8-81.2%), respectively. A very good response to MCS occurred in 3 patients (95% CI: 10.8-60.3%) from the rTMS responsive group while no patients (95% CI: 0-39.0%) had a very good response in the group that did not respond to rTMS (Fig. 4).

Anamnesis length positively correlated with the outcome in our cohort. This correlation is statistically significant ($p < 0.001$) upon exclusion of a single outlying data point for a 73-year-old man with 32 years of pain duration, initial VAS of 8 and 43.8% VAS improvement after stimulation (Fig. 5).

We were forced to remove the system in one patient in the NFP group three months after implantation due to infection; we did not attempt to reimplant it. No other complications were found.

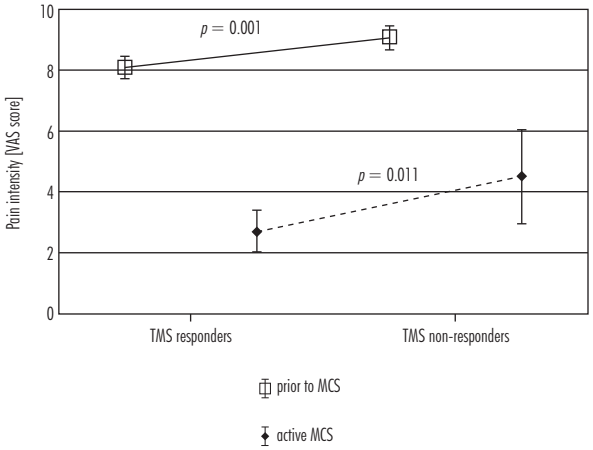


Fig. 4. Pain intensity (as measured on visual analogue scale, VAS) with and without stimulation depending on responsiveness to transcranial magnetic stimulation (TMS)

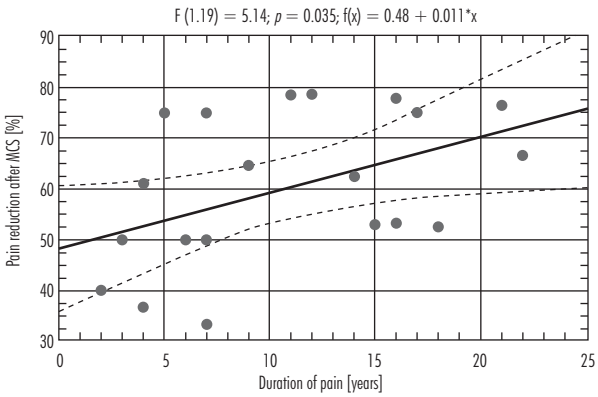


Fig. 5. Pain reduction on visual analogue scale relative to the length of pain history. Correlation is statistically significant when one outlying observation was excluded (73-year-old man with pain duration of 32 years, 8 pts. baseline pain intensity and 43.8% pain reduction after motor cortex stimulation [MCS], $p < 0.001$).

Discussion

Great suffering of the patients as well as inefficient pharmacotherapy result in attempts to treat neuropathic pain with minimally invasive MCS. However, lack of qualification standards for symptomatic treatment of neuropathic pain with MCS results in inconsistent and small observational case series. At first, Meyerson and Tsubokawa treated post-stroke pain syndromes and neuropathic trigeminalgia with MCS. When qualified for surgery with no response to pharmacotherapy, MCS might be considered a treatment of choice for these patients. In the treatment of pain with different aetiologies, such as deafferentation pain, MCS should be considered only for cases with previous failures of other surgical modalities such as dorsal root entry zone (DREZ)-tomy [14-19].

A qualification process for MCS necessitates a proper diagnosis of neuropathic pain and confirmation that all pharmacological modalities have been exhausted. Anamnesis should be at least two years long and pain intensity should exceed 6 on a 10-point VAS scale. Pharmacological tests (ketamine test in particular) and rTMS have prognostic value in the qualification process. The importance of rTMS as a prognostic factor in the treatment of neuropathic pain has been confirmed, but a lack of response to rTMS preoperatively should not disqualify patients with neuropathic pain from MCS. Additionally, adulthood should be one of the conditions for surgical treatment with MCS.

Negative prognostic factors for MCS implantation include paresis or paralysis and complete loss of superficial sensation within the pain region. Atypical facial pain, personality and psychiatric disorders, epilepsy or

the presence of another stimulation system are contraindications for MCS. Psychological examination is of crucial importance in order to eliminate any patients with psychogenic pain syndromes that could imitate neuropathic pain. Intraoperative analysis of somatosensory or motor evoked potentials is not performed during implantation of MCS for DP related to avulsion injury; the identification of relevant cortical regions is based on MRI and fMRI [20-24], as in our cases.

Pain reduction by ≥ 50% when assessed with the VAS should be considered as a therapeutic success although no uniform protocol for treatment efficacy evaluation for patients with neuropathic pain exists. The efficacy of neuropathic pain treatment with MCS varies from 15 to 90%, relative to the group at hand, with the best results achieved in the NFP group. Accordingly, the follow-up period may influence the outcome, as up to 40% of patients lose the positive effect of stimulation over a year [6,13,25-27].

Stimulation parameters during the postoperative period are programmed in order to achieve the effect of sub-threshold motor stimulation. The ability to modulate stimulation amplitude allows the patients to change it depending on the intensity of pain. The most common complications of MCS treatment include epileptic seizures (during initial stimulation programming), infections, epidural haematoma and skin erosion over the implant [9,28].

Conclusions

1. Motor cortex stimulation is a safe, reversible symptomatic treatment for neuropathic pain of various aetiologies.
2. Transcranial magnetic stimulation response is a positive prognostic factor.
3. Neuropathic facial pain shows the highest response rate to cortical stimulation while deafferentation pain has a worse prognosis.

Disclosure

Authors report no conflict of interest.

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