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Special Feature Article

Possibility of Neuromodulation for Treatment-resistant Depression

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Abstract

Currently, the number of patients diagnosed with depression is estimated to be approximately 1.27 million in Japan, and when we include the number of patients with depression but if those who have not undergone psychiatric treatment are included, it would be approximately 2.5 million in total. Furthermore, approximately 30% of them are said to be treatment-resistant, and thus making depression is becoming a national disease. Among them, these patients, those with severe depression usually need hospitalization in psychiatry, but require admission to a psychiatric ward. However, the urgent issue in psychiatric clinical practice for depression is that although the severity of depression itself is mild to moderate, some of these patients show a refractory and prolonged depression, that is termed "treatment-resistant", which does not improve depressive symptoms with conventional treatment. As a promising therapeutic method for such a group of patients, in recent years, neuromodulation treatment including repetitive transcranial magnetic stimulation (rTMS) has attracted attention and its possibility is expected as an alternative therapeutic strategy. In this article, I would like to outline the effectiveness of neuromodulation for treatment-resistant depression.

Keywords: treatment-resistant depression, neuromodulation, repetitive transcranial, magnetic stimulation (rTMS), deep TMS, magnetic seizure therapy (MST)

Introduction.

The number of patients with "treatment-resistant depression" is increasing year by year as the number of depressed people increases worldwide. However, the definition of "treatment-resistant depression" is still ambiguous clinically, and there is no consensus on the definition. The term "treatment-resistant depression" generally refers to "a case in which depressive symptoms do not improve despite the use of sufficient doses of two or more different antidepressants for a period of six weeks or longer. In this article, the author presents the possibility of neuromodulation for treatment-resistant depression, based on his presentation at a symposium titled "New treatment strategies when conventional pharmacotherapy fails: Challenges for intractable psychiatric symptoms" at the 115th Annual Meeting of the Japanese Society of Psychiatry and Neurology. The possibility of neuromodulation for treatment-resistant depression" will be outlined.

I. What is Neuromodulation?

In recent years, the term "neuromodulation" has been used frequently in the central nervous system field. Neuromodulation refers to "a treatment method that reversibly modulates neural activity and modifies or improves its function by administering electrical or magnetic stimulation or drugs to the nerves.) 4) Neuromodulation, by definition, includes invasive intervention methods such as implantable devices, but in the psychiatric field, it usually refers to non-implantable, non-invasive approaches. In psychiatry in particular, repetitive transcranial magnetic stimulation (rTMS) and deep transcranial magnetic stimulation (deep TMS) using H-coils are gradually being applied clinically, especially in Europe and the United States. For severe cases, magnetic seizure therapy (MST) has been used in clinical studies.

II. rTMS Therapy

In Japan, the NeuroStar TMS system (Neuronetics, Inc.) was approved by the Japanese regulatory authorities in September 2017 and was included in the insurance coverage in June 2019. In addition, the Brainsway TMS system (Brainsway Ltd.) received regulatory

approval in January 2019. In addition, the MagPro system (MagVenture, Inc.) and Magstim TMS Therapy (Magstim Company Ltd.) are being used for clinical research in Japan. The overall outcome of acute rTMS for patients with treatment-resistant depression has been reported to be a response rate of approximately 50% and a remission rate of approximately 30%, with baseline depressive symptom scores improving by less than half using a standard protocol approved by the U.S. Food and Drug Administration (FDA).18) In addition, the effect on cognitive function is not clear.) As for the effects on cognitive functions, it has been shown that cognitive functions, especially psychomotor speed, visual scanning ability, and set switching ability, may be moderately improved15) .

The indications for rTMS for depression are treatment-resistant depression that does not respond to pharmacotherapy or psychotherapy, and for pharmacotherapy, at present, it is preferable to treat moderate or severe depression that is ineffective after trying one or more antidepressants in sufficient doses and for a sufficient period of time18). On the other hand, urgent conditions such as psychotic symptoms, catatonia, and impending thoughts of death are not indicated. The most common adverse events associated with rTMS include pain at the stimulation site, discomfort due to stimulation-induced muscle contraction of the head and face, and toothache due to stimulation-induced vibration. The most common rTMS-related adverse events are pain at the stimulation site, discomfort due to muscle contraction of the head and face associated with stimulation, and toothache due to vibration associated with stimulation. As a very rare side effect, convulsive seizures and hypomania have been reported with a frequency of less than 0.1%18) .

III. Clinical usefulness of rTMS for depression

Slotema, C. W., et al. calculated the effect size of rTMS on depression from pre- and post-treatment data from 34 randomized controlled trials (RCTs), and conducted a meta-analysis comparing the effect size of rTMS with that of 6 ECT studies. Slotema et al. found that the effect size of rTMS compared with sham stimulation was 0.55 ($P < 0.001$), and the relative effect size of rTMS compared with ECT was -0.47 ($P = 0.004$).21)

In a systematic review and meta-analysis (25 studies: 1,288 depressed patients) comparing the efficacy and tolerability of rTMS and ECT for depression, Chen, J. J., et al. found the following: ECT was more effective, although not statistically significant,

than bilateral rTMS, low-frequency right-sided rTMS, and high-frequency left-sided rTMS. ECT was more effective than bilateral rTMS, low-frequency right-sided rTMS, and high-frequency left-sided rTMS, although the results were not statistically significant. Left lateral prefrontal rTMS was not statistically significant but showed higher efficacy than the other modalities (ECT, bilateral rTMS, right lateral rTMS). In terms of tolerability, right-sided rTMS was better tolerated than ECT, bilateral rTMS, or left-sided rTMS, although this was not statistically significant. By cumulative probability, ECT was the most effective treatment (ECT: 65%, bilateral rTMS: 25%, right-sided rTMS: 8%, left-sided rTMS: 2%), and right-sided rTMS was the best tolerated treatment (right-sided rTMS: 52%, bilateral rTMS: 17%, left-sided rTMS: 16%, ECT: 14 %)5).

Regarding the clinical efficacy of rTMS in various protocols, Brunoni, A. R. et al. conducted a network meta-analysis of acute rTMS treatment for depression (81 clinical studies: 4,233 depressed patients, 59.1% women, mean age 46 years) and found the following results3) . In a network meta-analysis of response rates, the odds ratios for sham stimulation were bilateral rTMS [odds ratio (OR): 3.96, 95% confidence interval (CI): 2.37-6.60], left high-frequency rTMS (OR 3.07, 95% CI OR: 3.07, 95% CI: 2.24-4.21), seater burst rTMS (OR: 2.54, 95% CI: 1.07-6.05), right low-frequency rTMS (OR: 2.37, 95% CI: 1.52-3.68), while for tolerability, all intervention methods had similar acceptance rates as sham stimulation.

IV. Clinical usefulness including neuromodulation treatments other than rTMS

In addition, Mutz, J. et al. recently conducted a systematic review and meta-analysis comparing the efficacy and tolerability of neuromodulation as an acute treatment for depression.) The study included ECT, rTMS, accelerated TMS, priming TMS, deep TMS, synchronized TMS, theta burst stimulation (TBS), MST, transcranial direct current stimulation (tDCS The primary endpoint was response (effective). The primary endpoints were response (efficacy) and treatment discontinuation (acceptability), with ORs with 95% CIs comparing each intervention. The study included a total of 113 trials (262 treatment arms: 6,750 patients, mean age 47.9 years, 59% female), and included patients with major depressive disorder and bipolar depression who met the inclusion criteria. A network meta-analysis found that 10 of the 18 treatment interventions were associated with higher treatment response compared

with sham stimulation. Specifically, bilateral temporal ECT (summary OR: 8.91), high-dose right unilateral ECT (OR: 7.27), priming TMS (OR: 6.02), MST (OR: 5.55), bilateral rTMS (OR: 4.92), bilateral TBS (OR: 4.44), low-frequency right-sided rTMS (OR: 3.65 (OR: 5.55), intermittent TBS (OR: 3.20), high-frequency left-sided rTMS (OR: 3.17), and tDCS (OR: 2.65) interventions showed a higher response than the sham stimulation intervention. In a network meta-analysis of the active intervention groups, bilateral temporal ECT and high-dose right unilateral ECT were associated with higher treatment response. In a network meta-analysis between the active intervention groups, bilateral temporal ECT and high-dose right unilateral ECT were associated with higher treatment response, and all interventions were at least as receptive as sham stimulation.)

V. Effects of rTMS treatment to the prefrontal cortex on cognitive functions in various psychiatric disorders

The authors also recently conducted a systematic review of the effects of rTMS treatment on the cognitive profiles of depression, schizophrenia, and Alzheimer's disease. 31 studies met the inclusion criteria, 15 for depression, 11 for schizophrenia, and 5 for Alzheimer's disease. dementia was included in 5 studies.

Of these, six studies showed improvement in executive function, and none reported adverse events related to cognitive function. Although the type of cognitive function tests, rTMS stimulation parameters, and subject heterogeneity in previous studies limit the ability to show consistent results, the study still suggests that rTMS treatment of the prefrontal cortex may improve executive and attentional function, especially in some depressed patients. The results of this study are summarized in Table 1. However, for schizophrenia and Alzheimer's disease, the effects of rTMS treatment on cognitive function varied from study to study, indicating that further clinical research, including systematic assessment of cognitive function, is needed in the future9) .

VI. Usefulness of TBS treatment for depression

Berlim, M. T. et al. conducted a meta-analysis on the treatment outcomes of five RCTs (221 depressed patients) of TBS for depression.1) TBS is a new neuromodulation treatment for depression, which was developed to mimic the more physiological EEG rhythms of the human brain compared to conventional rTMS. Berlim, M. T., et al. conducted a meta-analysis of the outcomes of five RCTs (221 depressed patients) of TBS for depression, using

pre- and posttreatment changes in Hamilton Depression Rating Scale (HAM-D) score, response rate, remission rate, and dropout rate as indicators.1) The results showed that the HAM-D score was significantly higher than the HAM-D score in the pre- and posttreatment periods. 1) The results showed that the pooled Hedges' g for the change in HAM-D score before and after treatment was 1.0 (P=0.003), and TBS treatment showed significantly greater efficacy than sham stimulation. Furthermore, TBS showed a higher response rate than sham stimulation (35.6% vs. 17.5% in the TBS group, P=0.005), while the dropout rate (4.2% vs. 7.8% in the TBS group, P=0.5) was similar between the two groups. Subgroup analysis showed that among TBS protocols, bilateral TBS and unilateral intermittent TBS may be the most promising protocols.)

VII. Comparative validation study of the efficacy of TBS and rTMS treatment

The traditional FDA-approved high-frequency left-sided rTMS treatment protocol takes 37.5 minutes per session, while the novel TBS treatment protocol takes only 3 minutes per session. Therefore, there is a significant difference in time burden for therapists and subjects between the two treatment interventions. Considering the efficiency of the treatment and the logistics of the therapist and treatment equipment, TBS is by far the more rational intervention method. Although the results of the above meta-analysis suggested that TBS treatment is more effective than sham stimulation for depression, there were no clinical studies comparing the efficacy (efficacy, safety, and tolerability) of TBS treatment and conventional rTMS treatment. Blumberger, D. M., and colleagues at the Centre for Addiction and Mental Health, University of Toronto, led the study of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D) study and obtained the following results2) . 2) The author participated in the study as a therapist member of the research group and carried out the study. This clinical study was conducted as a multicenter, randomized, noninferiority trial at an academic research institution in Canada. Subjects were 18 to 65 years of age with treatment-resistant depression or intolerance to at least two antidepressants, who received stable antidepressant treatment for at least four weeks and had a HAM-D17 score of 18 or higher. Subjects were randomized to 1:1 10 Hz-rTMS and intermittent TBS to the left dorsolateral prefrontal cortex for a total of 20 to 30 TMS interventions. The treatment was open-label to the subjects, but remained blind

to the investigators and raters. The primary endpoint was the change in HAM-D17 score, with a difference margin of 2.25 points between the two groups to prove non-inferiority. The primary endpoint was the change in HAM-D17 score, with a margin of difference of 2.25 points between the two groups to demonstrate noninferiority. 205 patients were assigned to the 10 Hz-rTMS group and 209 to the intermittent TBS group. 192 (94%) and 193 (92%) patients, respectively, were evaluated for the primary endpoint after 4 to 6 weeks of treatment. In terms of TMS-related pain, the intermittent TBS group had a verbal analogue scale score of 3.8, compared with 3.8 in the 10 Hz-rTMS group. The intermittent TBS group had a verbal analogue scale of 3.8, whereas the rTMS group had a verbal analogue scale of 3.4, indicating that the intermittent TBS group experienced more pain. There was no significant difference in dropout rate between the two groups [10 Hz-rTMS: 13 (6%)/205 patients; intermittent TBS: 16 (8%)/209 patients; P=0.60]. The most common adverse event was headache during stimulation in both groups [10 Hz-rTMS: 131 (64%)/204 patients; intermittent TBS: 136 (65%)/208 patients]. The most common adverse events in both groups were headache during stimulation [10 Hz-rTMS: 131 (64%)/204 patients, intermittent TBS: 136 (65%)/208 patients], indicating that intermittent TBS treatment for treatment-resistant depression is as effective as conventional rTMS treatment.2) With these results, TBS treatment for depression was officially approved by the FDA in August 2018.

VIII. Trajectories Analysis of Responsiveness to TMS Treatment for Depression

Kaster, T. S., and colleagues at the Department of Psychiatry, University of Toronto, conducted a trajectory analysis of the response to rTMS treatment of the left prefrontal cortex from the THREE-D study data and identified clinical characteristics at baseline that were associated with treatment responsiveness.) Trajectory analysis of treatment responsiveness by group-based trajectory modeling using the HAM-D17 score identified the following four trajectories. (1) non-response (N=43, 11%); (2) rapid response (N=73, 19%); (3) severe linear response at baseline (N=118, 30%); and (4) mild linear response at baseline (N=154, 40%). In addition, the study was able to detect significant differences in response and remission rates between each trajectory at one week after the start of treatment. There was no clear association between treatment protocol and treatment response trajectory. In

particular, high HAM-D17 score and high QIDS-SR score at baseline were associated with treatment non-response trajectories, while high age, low QIDS-SR score and benzodiazepine non-use were associated with rapid response trajectories12).

IX. Clinical Applications of Deep TMS

Deep TMS is a minimally invasive neuromodulation technique that uses a special helmet-shaped coil called H-coil to directly stimulate the brain to a depth of about 4 cm from the head surface. To date, various types of H-coils have been developed to target different brain regions. In particular, the H1-coil was approved by the FDA in January 2013 as a neuromodulation treatment for drug-refractory depression.

Kaster et al. conducted a clinical study with an RCT design in patients aged 60-85 years with treatment-resistant depression to evaluate the efficacy, tolerability, and effects on cognitive function of high-dose deep TMS (H1-coil, 6012 pulses, 18 Hz, 120% RMT) for geriatric depression11).). The H1-coil targets the dorsolateral and ventral lateral prefrontal cortices. The author also participated in this study as a therapist member. The primary endpoint of this study was the remission rate of depression based on the analysis of treatment attempts (ITT analysis). Fifty-two subjects participated, 25 in the active depression TMS group and 27 in the sham H1-coil group. The remission rate was significantly higher in the active deep TMS group than in the sham H1-coil group (40.0% in the active group vs. 14.8% in the sham group), and the number needed to treat (NNT) was 4.0 (95% CI: 2.1-56.5). Deep TMS did not have any adverse effects on executive function. The adverse event profile was comparable between the active and sham groups, except for headache during stimulation in the active group (16.0% vs. 0% in the sham group). The results of this study indicate that high-dose deep TMS is a safe, well-tolerated, and effective neuromodulation treatment for geriatric depression11) .

X. Clinical Applications of MST

MST is a new neuromodulation treatment technique that is an alternative to ECT. MST is a new neuromodulation technique that can be used as an alternative to ECT. Similar to ECT, MST induces therapeutic seizures under general anesthesia, but compared to ECT, MST has a similar antidepressant effect with much less adverse effects on cognitive function13-17).

We report the world's first case of successful treatment of adolescent refractory bipolar depression with MST, which the authors experienced during

their previous study at the Centre for Addiction and Mental Health, Department of Psychiatry, University of Toronto.) The patient participated in an open-label study of treatment-resistant depression (NCT01596608)6) and was treated with acute MST. MST treatment in this study used twin coils with each coil center adapted to the F3 and F4 sites; MST output parameters used were 100% mechanical output at 100 Hz and a protocol that gradually increased stimulation duration in response to convulsive elicitation. Depressive symptoms were assessed with the HAM-D24, and cognitive function was assessed with a comprehensive neuropsychological examination. The patient achieved remission after 18 sessions of acute MST treatment and remained stable for 11 months. There was no apparent impairment in cognitive function except for some autobiographical memory impairment. This case report suggests that MST treatment may be a safe, well-tolerated, and effective treatment for refractory bipolar depression in adolescents.)

Conclusion.

In this article, we discuss neuromodulation therapy, which is becoming a new treatment strategy in psychiatry, mainly for treatment-resistant depression. We hope that neuromodulation therapy will become one of the treatment options in normal psychiatric practice in Japan.

There are no conflicts of interest to be disclosed in relation to this paper.

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