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Application of Deep Brain Stimulation for Treatment-resistant Obsessive Compulsive Disorder: Current Status and Future Perspectives in Japan

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Abstract

As in many Western countries, deep brain stimulation (DBS) is already being used daily in Japan to clinically treat neurological diseases such as Parkinson's disease, essential tremor, and dystonia. Additionally, in both Europe and the United States, numerous case reports as well as multicenter randomized controlled trials have examined its use for treatment-refractory mental illnesses such as obsessive compulsive disorder (OCD) and major depressive disorder. Based on a number of the reports, the European Union (EU) and the USA Food and Drug Administration (FDA) granted limited approval of DBS for treatment-resistant OCD in 2009. Furthermore, a systematic review and meta-analysis in 2015 showed that DBS therapy for patients with treatment-resistant OCD had efficacy and was safe. Unlike the EU and the USA, DBS is not used to treat OCD or other psychiatric disorders in Japan, even though people with treatment-resistant OCD and their physicians and families urgently need additional treatments. This situation results from the "Resolution of total denial for psychosurgery," which the Japanese Society of Psychiatry and Neurology adopted in 1975. We believe that the appropriateness of using DBS for treating psychiatric disorders including OCD should be considered after thorough discussion and consideration based on accurate and objective understanding. Currently, the field of psychiatry in Japan seems to lack scientific consideration as well as scientific understanding in this area. Under these circumstances, we hope that this review article will help psychiatrists and other relevant parties in Japan to gain an accurate and scientific understanding of DBS.

Keywords: deep brain stimulation, neuromodulation, obsessive compulsive disorder, stereotactic neurosurgery, treatment resistant

Introduction

Although deep brain stimulation (DBS) is already used in daily clinical practice for treating neurological diseases such as Parkinson's disease, essential tremor, and dystonia, it is not familiar to psychiatrists in Japan. However, the application of DBS in the clinical treatment of psychiatric disorders such as treatment-resistant obsessive compulsive disorder (OCD) and major depression has been described in numerous case reports, case series, and multicenter randomized controlled clinical trials in Europe and the United States. This review paper gives an overview of DBS and the current status of DBS application for OCD.

Overview of DBS

DBS is a neuromodulatory technique that was first developed around 1960 as a treatment for intractable pain. In subsequent years, DBS has attracted attention as a treatment for loop circuit disorders in the brain, and has been used to treat Parkinson's disease, essential tremor, dystonia, and other involuntary movement disorders. In Japan, it was first approved by the Pharmaceuticals and Medical Devices Agency (PMDA,

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the Japanese Food and Drug Administration [FDA]) as a treatment for intractable pain in 1986, and then approved as a treatment for involuntary movement disorders in 2000. During the last two decades, intractable diseases have been studied worldwide to determine if they are loop circuit disorders of the central nervous system, and DBS has been tested as a treatment for those disorders in which it has been assumed. Currently, more than 160,000 people have received this treatment across the globe.[1)]

DBS requires an electrode to be placed deep in the brain. Typically, electrodes are coaxially placed on a lead wires and inserted into the nerve nucleus of the brain by stereotactic brain surgery. The electrodes are connected to a neurostimulator, which is embedded in the precordial area of the chest. The neurostimulator acts like a pacemaker to electrically stimulate the brain when needed by sending current to the electrodes. The contact area of the electrodes is approximately 6 mm^2, even for concentric electrodes, and the intensity of electrical stimulation is quite low, with a current of approximately 3 mA and a charge density of 30 $\mu C/cm^2$. Therefore, the electrical stimulation only extends to the area just around the electrodes. Therefore, DBS is expected to be effective against diseases that feature a loop circuit disorder of the brain in which continuous stimulation at one point within the loop can bring brain activity back into balance. Conversely, DBS is not suitable for pathological conditions in which a large number of brain regions need to be targeted. Importantly, the concept of DBS is totally different from that of electroconvulsive therapy, which can reset the entire brain by applying powerful electrical stimulation.

Stereotactic Neurosurgery

In a typical DBS surgery, a frame for stereotactic brain surgery (stereo frame) is set on the head and the electrode is implanted with the help of magnetic resonance imaging (MRI)-based image navigation. Often, all surgical operations are performed under local anesthesia, which means that the patient is awake. However, because of recent advances in anesthesia and functional imaging techniques, surgical procedures can be performed under general anesthesia to reduce patient distress. Functional MRI and tractography assessed with diffusion tensor imaging have been used to set electrodes based on the identification of neural circuits and nerve fiber bundles. At our institution, patients are awakened only when identifying the target and the subsequent implantation and fixation of the electrode using MRI navigation. During the other surgical procedures, such as setting stereo frames, creating bar holes, and setting deep brain stimulators, we use general anesthesia or sedation. Overall, DBS surgical complications are infrequent; among more than 200 cases reported since 2012, symptomatic intracranial hemorrhagic complications associated with DBS have a frequency of 0–1.8%. For more details related to complications, please refer to the 3rd edition of the Treatment Guideline for Stereotactic and Functional Neurosurgery, published in 2019.[2)]

Efficacy and Safety of DBS for Treatment of OCD

In 1999, the Lancet published a study by Nuttin et al. in which DBS was applied to the anterior limb of internal capsule to treat four cases of treatment-resistant OCD.[3)] Even in these treatment-resistant cases, 2 weeks of electrical stimulation with DBS improved anxiety, obsession, obsessive compulsive, and ritualistic behaviors in three of the four patients. Actionably, symptom relapse due to discontinuation of stimulation was observed. Furthermore, they observed effects of DBS on psychiatric symptoms even after repeated a combination of single stimulation and its discontinuation in a double-blinded manner. Based on these results, they suggested that DBS had the potential to replace irreversible capsulotomy, which was the current option at that time for treatment-resistant OCD.[3)]

In the following years, a number of studies reported the effects of using DBS in cases of treatment-resistant OCD, and a systematic review and meta-analysis was eventually published in 2015.[4)] As a result of this systematic review and meta-analysis, 31 research reports covering 116 cases were identified between 1999 and 2014. The meta-analysis of 66 cases revealed that assessments on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) improved by 45.1% on average, and by 35% or more in 60% of cases (responders). The target sites in these reports were mostly around the striatum (including the anterior limb of the internal capsule and nucleus accumbens), 27 in the subthalamic nucleus, and 6 in the hypothalamus. Although five patients dropped out, the adverse events were generally mild, transient, and reversible. The adverse events related to surgery (intracerebral hematoma, 2.6%; wound infection, 4.3%; headache, 6%), the device (extension lead discomfort around neck and ear, 8.6%; stimulator discomfort in chest and abdomen, 1.7%; extension lead and wire breakage, 2.6%), and irritation (hypomanic symptoms, 19.8%; disinhibition, 6%; worsening anxiety symptoms, 21.6%; forgetfulness and memory difficulty, 7.8%; stomach pain/dizziness/nausea, 6.0%). Based on these results, the authors confirmed that DBS could be an alternative to irreversible lesion

for treatment-resistant OCD. Moreover, to establish the best surgical procedure, optimized stimulation conditions, and predictors of responsiveness, additional large-scale well-designed randomized controlled trials should be conducted. Based on the favorable outcomes, Europe and the USA approved DBS for treatment-resistant OCT in 2009 (as CE Mark in the European Union (EU) and as a Humanitarian Device Exemption by the FDA in the United States).

Neural Mechanisms of DBS that Underlie Improved OCD Symptoms

As mentioned above, DBS is effective for a loop circuit disorders in the brain because they can be effectively modulated by continuously stimulating a location within the loop. However, it is not suitable for treating pathological conditions that require brain activity to be altered at a large number of regions. Additionally, DBS is different from methods such as electroconvulsive therapy that reset the entire brain by applying strong electrical stimulation. The brain pathophysiology of OCD is thought to involve hyperactivity in the cortico-striato-thalamo-cortical (CSTC) loop circuit. Conceptually, DBS directed toward target sites that surround this loop, such as the striatum and thalamus, can suppresses the hyperactivity in the CSTC loop, which reduces OCD symptoms.[5]

Based on this hypothesis, a research group at the Academic Medical Center (AMC) in Amsterdam has been using neuroimaging techniques such as functional MRI and single photon emission computed tomography (SPECT) to study OCD. Figee et al. found that hypoactivity of the nucleus accumbens and excessive enhancement of functional connectivity between the nucleus accumbens and the prefrontal cortex during a reward task were observed in patients with OCD. While these patterns of brain dysfunction were also observed when DBS stimulation was turned off, they reported that normalization of the dysfunction and reduced low-frequency EEG oscillations over the frontal lobe during symptom provocation was observed when the stimulation was turned on.[6] Furthermore, using SPECT and measurements of plasma homovanillic acid levels, they showed that both acute stimulation for 1 hour and chronic stimulation for 1 year led to reduced binding potential of the dopamine D2/3 receptor in the putamen, which was accompanied by an increase in plasma homovanillic acid levels relative to unstimulated conditions. They suggested that these chemical changes in the central and peripheral systems represent the facilitation of dopamine release induced by DBS. Additionally, another study has shown that clinical symptoms improved more in the cases in which the binding potential of the D2/3 receptor around the electrode implant site was reduced.[7]

Understanding and Concerns about DBS for Mental Illness

With the approval of DBS treatment for OCD in Europe and the USA, and with the increase in the number of cases in which DBS has been used, three groups (i.e., individuals with OCD, psychiatrists, and psychotherapists who perform cognitive behavioral therapy) joined together to investigate what is known about DBS and the concerns in Sweden.[8] Consequently, in addition to information from academic sources such as scientific papers and acquaintances, all groups acquired information from the Internet, newspapers, and television. Among those with OCD, the most common concerns included adverse events related to stimulation, potential ineffectiveness, complications of surgery and anesthesia, personality changes, and changes in appearance. Among psychiatrists, the common concerns were patient resistance to neurosurgery, complications related to surgery and anesthesia, difficulty in identifying cases suited for DBS, and ethical concerns about neurosurgery. Among the cognitive behavioral therapists, the common concerns were complications of surgery and anesthesia, potential personality changes, ethical concerns about neurosurgery, the likelihood of ineffectiveness, the criteria for when DBS can be used, and insufficient consideration of other treatments. A similar survey conducted in Japan would be interesting because there are some predictable results and some surprising results in this report from Sweden.

Application of DBS for OCD in Japan and Our Institution

Similar to other countries such as the USA and those in the EU, Japanese people with treatment-resistant OCD (and their families) have an urgent need for other treatments. Daily life is often seriously affected in severe and treatment-refractory cases of OCD. In severe cases, patients with OCD might wash their hands or body over-and-over in the same order for several to 24 hours per each bathing. In such cases, they tend to avoid bathing as much as possible, sometimes as much as once a year. When family members are involved in their compulsions, people with severe OCD cannot continue to live with them. Patients who cannot leave their bed because of fear of pollution use diapers even in adulthood or adolescence. Despite DBS treatment-related recovery from similarly severe and treatment-refractory OCD in the EU and USA, DBS cannot be used to treat OCD or

any other psychiatric disorders in Japan. During the 1960s and 1970s, a global campaign that rightly opposed lobotomy gained popularity in Japan, as well as student and medical intern movements. Consequently, the Japanese Society of Psychiatry and Neurology adopted the "Resolution of total denial for psychosurgery" in 1975.[9] Thus, any type of neurosurgery for patients with psychiatric disorders has been taboo in Japan. In collaboration with Kenji Sugiyama (a co-author of this article), Norio Mori and colleagues at Hamamatsu Medical University School of Medicine have developed a research plan for the first application of DBS for treatment-resistant OCD in Japan. The ethical committee of our University approved the research plan in 2015. Since 2016, Hidenori Yamasue (the other co-author of this article) replaced Mori and continued the collaboration with Sugiyama. Together, we consulted the PMDA of Japan and Medtronic CO to discuss the possibility of future approval of DBS for OCD treatment in Japan and how to obtain such approval. During the course of our collaboration, we noticed that a more extensive and scientific understanding is needed from the committee of psychiatry in Japan. Toward this aim, we therefore recently published two review articles in Japanese on the use of DBS for treating psychiatric disorders.[10,11]

Summary and Future Perspectives

In Europe and the United States, limited approval of DBS for treatment-resistant OCD was made by the EU and US FDA in 2009. A meta-analysis of its efficacy and safety has already been reported in 2015, and the outcomes were favorable. However, DBS has never been used to treat OCD or any other psychiatric disorder in Japan, and there seems to be no prospect of future implementation. This is despite the urgent need for additional treatments for individuals with treatment-resistant OCD and their families. We believe that the appropriateness of DBS as optional treatment for certain psychiatric disorders, including OCD, should be considered after thorough discussions based on accurate and objective understanding. Japan seems to currently lack enough scientific consideration and scientific understanding, particularly in the field of psychiatry. Under these circumstances, we hope that this review article will help psychiatrists and interested parties in Japan to gain an accurate and scientific understanding of DBS.

Conflict of Interest Disclosure

KS has declared his conflicts of interest to the Japanese Neurosurgical Society. There are no conflicts of interest for any person or organization affiliated with this work.

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