Deep brain stimulation and aggression

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Although deep brain stimulation (DBS) is an established neurosurgical treatment option for various movement disorders, the origins of DBS lie in the earlier use of electrical stimulation via implanted depth electrodes to study and treat emotional and behavioral disorders, which even included patients with aggressive behaviors.7 In their article, Torres and colleagues9 describe their experience using DBS targeting the posteromedial hypothalamus (PMH) in 4 male and 2 female patients who had severe chronic medication-resistant aggressiveness. The patients were 17–48 years old at the time of surgery. All of the patients had significant intellectual and neurobehavioral disabilities that necessitated institutionalized care, had had daily uncontrollable aggressiveness for at least 5 years, and had not responded to 5 or more medication trials. One patient had normal development until age 14, when his behavior problems commenced. A temporal lobe arteriovenous malformation and complex partial seizures were subsequently diagnosed. The other 5 patients had autism spectrum disorders and moderate-to-severe mental retardation, with developmental and behavioral problems that were apparent by age 2. Two of these 5 patients had had perinatal hypoxia, and 2 had seizure disorders. The final approval for DBS surgery was given after an extensive multidisciplinary evaluation, local ethics committee review, and informed consent from the patients’ parents or legal guardians.

The PMH target was first localized using stereotactic procedures and then tested with microelectrode recordings and stimulation. Final electrode placement was established based on physiological responses (electrocardiographic, cervical muscle electromyographic, and electroencephalographic activity). Low-frequency low-voltage stimulation was started within days of the surgery. Adverse effects with initial stimulation were assessed by monitoring the patients’ heart rate, blood pressure, and electrocardiographic and electroencephalographic activity. Follow-up visits were scheduled for 1 and 3 months after surgery and every 6 months thereafter. Self-aggression, outward aggression, general aggressiveness, and asocial behavior were rated using the Inventory for Client and Agency Planning (ICAP) before surgery and at subsequent visits. Laboratory studies (levels of lipids, proteins, and various hormones), body weight, and sleep patterns also were monitored. Regardless of therapeutic response, the stimulation frequency and voltage were gradually increased during the 2nd year of DBS (while other stimulation parameters were adjusted to avoid exceeding a predetermined maximum charge density).

Outcomes compared to baseline were reported only for the patients’ last follow-up visit (6–82 months after surgery). One patient died following a stroke 6 months after DBS surgery. Her family noted a progressive reduction in violent attacks during the period between surgery and the stroke. A second patient died nearly 3 years after DBS surgery but had no apparent benefit from DBS. Neither death was believed to be related to DBS. Of the remaining 4 patients, 3 showed significant improvements on ICAP measures of self-aggression, outward aggression, and general aggressiveness, with improvement noted from the 1st month of stimulation. One patient showed a significant improvement on self-aggression but not the other measures. There was no improvement for any patient on the ICAP measure of asocial behavior.

Subsequent increases in DBS stimulation frequency or voltage did not appear to result in increased therapeutic effects or adverse effects. Seizure frequency reduction was noted in one of the 3 patients with seizure disorders. Sleep patterns improved in 3 patients. Weight gain occurred in 3 patients and weight loss in 1 patient. There were no significant changes on laboratory measures.

The apparent positive benefits, tolerability, and safety of PMH DBS demonstrated in this study should be considered in the context of several important methodological limitations: small sample size, limited set of clinical assessment measures, allowance of postsurgical medication changes, lack of sham control, and use of unblinded assessments.

A small sample size makes it impossible to identify and confirm any patient characteristics that might be associated with favorable or unfavorable outcomes. For example, it is notable that the oldest patient (who was 48 years old and did not develop significant behavior problems until age 14) had no apparent benefit from DBS. Moreover, the second-oldest patient (a 37-year-old woman) showed...
improvement in self-aggression but not in other aggressive behaviors. The remaining 4 patients, who had better overall responses to DBS, were much younger (17–23 years old). Hence, future studies should enroll patients with a broad age range to determine whether age of onset of aggression, duration of aggression, or age at implantation are significantly associated with outcome. Also, there might be important neurobiological sex differences that are relevant to pathological forms of aggression. Larger studies enrolling sufficient numbers of male and female patients to be able to assess the influence of sex on outcome with PMH DBS are necessary. Finally, a larger number of patients receiving PMH DBS obviously will permit a more thorough evaluation of the safety and tolerability of this treatment.

The ICAP, a standardized rating scale for evaluating the service needs of individuals with intellectual disabilities, comprehensively includes adaptive behavior subscales, maladaptive behavior indices, and maladaptive behavior subscales. For the present study, however, the authors reported on only a small number of selected maladaptive behavior measures from the ICAP, which rated certain behaviors as “aggressive” (that is, harmful to self or others, destructive to property, or disruptive) or “asocial” (that is, socially offensive or uncooperative). In addition to self-injury and aggression, individuals with severe autism spectrum disorders and/or intellectual disabilities have a wide variety of aberrant behaviors, psychopathology, and social/functional impairment. The study reported no effect of DBS on “asocial” behaviors, and the authors indicated that they did not expect to modify these behaviors with stimulation. I would not necessarily agree with this expectation, however, especially based on such a small number of patients. Long-standing (at least 5 years in these patients) severely disruptive behaviors, manifested by self-injury or aggression, are likely to affect other aspects of patients’ behaviors and functioning and to influence how others rate such behaviors and functioning. It would be useful to know whether a reduction in aggressiveness with PMH DBS results in any changes on other ICAP measures of adaptive and maladaptive behaviors, especially as they relate to the need for ongoing care and supervision, social and communication skills, personal and community living skills, and individual general functioning. It would also be important to determine whether these patients became more amenable to behavioral interventions as a result of DBS. In addition to the ICAP, future studies might include other measures that have been developed specifically for assessing self-injury, aggression, and violence.

The changes in sleep and weight seen in this study deserve further study using standardized measures of sleep, caloric intake, and activity. For example, wrist actigraphy could be used for monitoring sleep and activity levels in these patients. Sleep electroencephalographic studies would be technically difficult to perform in this patient population, but such studies would provide important information about sleep physiology with PMH DBS. Measuring energy expenditure directly in patients receiving PMH DBS also would be of interest, but this type of measurement is difficult in humans.

The authors state that “it seems unlikely that medica-
tion changes would account” for the observed therapeutic effects, but one wonders why prescribers made subsequent medication changes when patients’ aggressive behaviors began to improve early in the course of DBS. A more careful characterization of patients’ medication history, their medication regimen at the time of surgery, and the reasons for subsequent medication changes would have been helpful. Also, the authors only provide ICAP data at 2 time points—baseline and last follow-up visit. The authors state that “after the first months of DBS, the patients’ condition remained stable, with discrete fluctuations that were mostly related to stressful events.” How bad were these discrete fluctuations, and did they lead to changes in medication or other treatment? Reporting ICAP data at each follow-up visit, describing the nature of intervening “stressful events,” and quantifying medication changes would have been useful. As the authors note, a study design in which medications are kept constant would address this potential confounding factor. It would also be important to determine whether treatment with DBS is sufficiently effective to allow for safe reduction or even discontinuation of any medications.

The authors note that the PMH has been identified as a particular region of interest for the treatment of pathological aggression (using ablative procedures or DBS), but neural circuits involving connections between the mediobasal hypothalamus, amygdala, frontal cortex, and other regions are relevant. One limitation of this report is a lack of pretreatment and posttreatment neurobiological measures that could be used to characterize neural circuits of interest and to identify predictors of outcome. For example, functional MRI, PET, SPECT, magnetoencephalography, and diffusion tensor imaging would be potentially useful tools in future studies of PMH DBS for pathological aggression. The one patient who most clearly did not respond to DBS in this report had a temporal lobe arteriovenous malformation.

The design of future studies to confirm the effectiveness of PMH DBS for pathological aggression deserves careful consideration. A prospective randomized trial comparing active and sham DBS for a period of time, using independent blinded raters, followed by open-label treatment and extended follow-up is one approach. However, given the likely heterogeneity of the intended patient population, it is not clear to me that the randomized treatment groups would be sufficiently similar with respect to clinical and demographic characteristics to be able to fairly assess the effectiveness of DBS or predictors of outcome. Also, enrolling enough patients to achieve a sample size with sufficient power to evaluate outcomes of interest is potentially problematic and might require multicenter collaboration. As an alternative, a sham-controlled within-subject crossover design, using independent blinded raters, may be more feasible and clinically informative. Each patient could be randomized to receive an initial phase of double-blind sham or active treatment, then a second phase of double-blind crossover treatment, and finally extended open-label treatment. In their study, Torres and colleagues planned to titrate stimulation “dosing” upward during the course of follow-up, regardless of clinical benefit. Because they noted an improvement