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Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy

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Summary

Objectives. Experimental data and case reports of intractable epilepsy patients treated with deep brain stimulation (DBS) of the internal nuclei suggest a considerable anticonvulsant effect. We intended to describe the results of DBS on subthalamic nuclei and anterior thalamic nuclei (STN and ATN) from our patients and to evaluate the long-term efficiency and safety of DBS for controlling intractable epilepsy.

Methods. Six patients with refractory epilepsy and inadequate for surgery were implanted with DBS electrodes (3 in STN and 3 in ATN, respectively), switched on after a week of insertion followed by chronological observation. Seizure counts were monitored and compared with pre-implantation baseline.

Results. There was significant clinical improvement in respect of reduction of seizure frequency as well as the alleviation of ictal severity in almost patients. The mean reduction in seizure frequency was 62.3% (49.1% from STN vs. 75.4% from ATN). Except one patient (*patient 3*) with accidental infection on the right anterior chest, no complication or withdrawal of DBS was seen during our study.

Conclusion. DBS on STN and ATN demonstrated their clear efficiency and relative safety comparable or superior to previous studies during long term follow-up. Subsequent, well designed studies warrant the further increase of the knowledge about antiepileptic effect of DBS.

Keywords: Deep brain stimulation; subthalamic nucleus; anterior thalamic nucleus; refractory epilepsy.

Introduction

About thirty percent of the patients with epilepsy who are treated with antiepileptic drugs continue to have refractory seizures [16]. Respective surgery is considered as a therapeutic option if the seizures have a focal epileptogenic zone and presurgical evaluation clearly demonstrates that the area can be removed without causing neurological deficits. But, up to 40% of these cases are proven to be unsuitable for surgery because of the involvement of the eloquent areas or because of the bilateral or multifocal nature of the ictal onset [15]. Recently, a variety of brain structures that were thought to modulate cortical excitability have been stimulated for the purpose of improving seizure severity [3, 5, 6, 8, 11, 12, 17, 25–27]. Among them, the subthalamic nucleus (STN), which has a lot of accumulated human experience from Parkinson's disease (PD) for more than ten years and anterior thalamic nucleus (ATN) have been shown to be a safe and effective loci for controlling the intractable partial seizures from some patients [3, 5, 11, 12].

STN stimulation for epilepsy treatment has a basis from some experimental evidence of the subcortical network that influences cortical excitability – namely, nigral control of the epilepsy system (NCES) [9].

The role of ATN in the pathogenesis of seizure generalization is confirmed by the findings of increased metabolic activity in ATN during seizures and high frequency stimulation (HFS) of ATN and its afferent pathways can reduce seizures in the experimental animal studies [18–20].

Functional neuroimaging techniques have provided much information on the anatomic correlates of neurologic disorders [14], and there is growing evidence that different behavioral variables are represented differentially along distinct corticobasal ganglia circuits [1, 7]. We have previously shown that cerebral perfusion increase at the irritative zones of epilepsy patients is associated with favorable seizure reduction after HFS on STN in two cases of frontal lobe epilepsy (FLE) [24].

The aim of this study was to describe the results of chronic deep brain stimulation (DBS) on the deep nuclei (STN and ATN, respectively) from our patients and to evaluate the long-term efficiency and safety of DBS for controlling intractable epilepsy.

Patients and methods

Six patients with refractory epilepsy were implanted with DBS electrodes (three patients in the bilateral STN, the other 3 in bilateral ATN), switched on after a week of insertion and followed up for 2–30 months (mean 13.2 months). Two of STN DBS patients had a FLE (one with bilateral onset, the other with right sided onset). The other STN DBS patient had a temporal lobe epilepsy (TLE) of bilateral temporal onset. The surgical procedures and follow-up methods of STN DBS were described previously [24].

Two out of three patients with ATN DBS had non-lateralizing FLE. The last patient with ATN DBS was multifocal epilepsy from diffuse malformation of cortical development. We used Medtronic 3387 leads in ATN DBS and the target side was identified on each side by visual selection with reference to a standard stereotactic atlas under microelectrical recording of ATN and dorsomedial nucleus (DM) of thalamus. The EEG recording during the insertion of electrodes with or without external electrical stimulation (slow frequency; 5–10 Hz, intensity; 3–7 V, pulse width 90 μs) followed by connection of internal pulse generator (IPG) was performed as the method of STN DBS [24]. For chronic ATN HFS, we used a cycling stimulation on each side set to deliver 1 min on/5 min off, alternating left and right sides. Initially, monopolar current was provided with the pulse width of 90 μsec, and the frequency was set at 130 Hz. Stimulation parameter was adjusted for a satisfactory clinical response, determined individually for each patient.

Results

General results

After the chronic DBS, all of patients except one (patient 2) showed the >50% decrease in seizure frequency relative to the baseline value. Two patients with ANS DBS had seizure reduction >85%. Except one patient (patient 3), no major morbidity was developed during DBS period. Patient 3 had accidental, significant infection around the IPG insertion site and we stopped stimulation and removed the DBS device from him. No stimulation-induced side effects were observed. Families of three patients reported improvements in cognitive and behavioral status during daily living, and we previously reported the one example from patient 2 [24]. The overall results from our patient's seizure reduction ranged from 20 to 90.7%, with a mean of 62.3% (Table 1). In patient 3, the ratio was seizure frequency just before the removal of DBS devices compared with the baseline value.

Individual patients

Patient 1

A 23-year-old woman with global cognitive dysfunction was selected for STN DBS. Regardless of the previous respective surgery on the right frontal cortex with anterior callosotomy after a series of invasive study four years before, the refractory seizures were still continued. She displayed frequent bilateral asymmetric tonic seizures (left > right) with rare drop attacks, and mean seizure frequency was 15/month. Interictal EEG showed bilaterally independent and bilaterally synchronous generalized spike-and-wave discharges; maximal over the frontal regions with slight right side dominance and the ictal onset EEG showed generalized electrodecremental response followed by irregular spike-and-wave with briefly right hemispheric dominance, progressing to obscuration by movement artifacts. Her antiepileptic drugs (AED) were valproate, carbamazepine, topiramate and oxcarbazepine. Continuous monopolar STN stimulation started electrode at bilateral 3−, with the amplitude of 2.0 V and pulse width 60 μsec. The parameter of stimulation was changed according to the seizure frequency and intensity (1− to 3−, 2 to 3.2 V, 60 to 120 μsec), but no significant differences were seen with any of the parameter changes. At the moment of postoperative 30 month, the seizure had decreased to 56% of her baseline value and valproate and oxcarbazepine was successfully discontinued as well.

Patient 2

A 22-year-old male patient was admitted for DBS of the STN. Previously, he had undergone right cortical

Table 1. *Results of DBS of STN and ATN for Epilepsy in CMCK*

Patient	Localization of seizure onset	Site of insertion	Age (yr)	F/U (M)	Baseline seizure number/M	Seizure reduction
1	bilateral frontal, poorly localized	STN	23	30	15	56%
2	right frontal, diffuse	STN	22	18	75	20%
3	bilateral independent temporal	STN	14	loss d/t infection	42	71.4% (postop. 1 M)
4	bilateral anterior frontal	ATN	28	10	15	85.7%
5	bilateral frontal, poorly localized	ATN	23	6	15	90.6%
6	multifocal, poorly localized	ATN	14	2	450	50%
	average		20.7	11.2	102	62.3%

CMCK Catholic medical center of Korea, *STN* subthalamic nucleus, *ATN* anterior thalamic nucleus, *d/t* due to, *postop.* postoperative.

resection to relieve the frequent, brief hypermotor seizures with fencing posture that was suspected to originate from the right supplementary motor area (SMA). Interictal spikes were found in the right hemisphere with a right frontal dominance and during ictal onset period, the brief polyspikes or fast activity on both fronto-central areas (R > L, FC2 max) were followed by severe movement artifacts. However, he showed little clinical improvement after incomplete resection of the extensive epileptogenic zone. The seizure frequency was 2.5/day on the average despite of six AED medications. Bilateral continuous STN stimulation with the parameter (both 1−, 0.8 V, 130 Hz, 60 μsec) was started. Regardless of the various stimulation parameter (monopolar to bipolar, 0.8 V to 3 V, 60 μsec to 90 μsec), his seizure frequency and intensity was not reduced significantly. The reduction rate of seizure frequency at the last visit was about 20% comparing to frequency at the pre-stimulation period.

Patient 3

A 14-year-old boy with global cognitive delay and frequent automotor and hypermotor seizures with secondary generalization from bilateral independent foci of temporal lobe was selected for STN DBS. His seizure frequency was 1–2 per day and not controlled with topiramate, lamotrigine, valproate and vigabatrine. After insertion of electrode, marked reduction of seizure frequency and intensity was found. The ratio of 71.4% seizure reduction was seen after 3 weeks switched on. But, at 5 weeks after insertion, unexpected inflammation and discharges around the wound site of IPG on the R anterior chest was detected. Immediate and massive antibiotic therapy for 2 weeks was in vain and removal of IPG and all the other hardware after 50 days from electrodes insertion. The causative organism was *Staphylococcus aureus* detected from his wound infection site of the right anterior chest.

Patient 4

A 28-year-old woman with frequent dialeptic seizure and intermittent automotor seizure was admitted for ATN DBS. Her interictal spikes were seen in both the anterior frontal and L fronto-temporal areas. Ictal onset was fast rhythm poorly lateralized and appearing maximal in both frontal areas, that ultimately builds up in L hemisphere with fronto-temporal maximum. She refused invasive surgery and subsequent resective surgery for fear of the possible neurological sequelae. Mean seizure frequency of pre-insertional state was once per two days, but after insertion of ATN electrodes, marked reductions of seizure frequency were found. Monopolar, bilateral stimulation on lead 2− was continued with intensity of initial 1.5 V to the last 2.4 V, and the other parameter was described above. Ten months after initiation of ATN DBS, her seizure frequency was still continued once per 2 weeks (85.7% reduction).

Patient 5

A 23-year-old man with previous craniectomy for the resection of medulloblastoma in the cerebellum was admitted for the control of his frequent intractable secondarily generalized seizures. The seizure frequency was 0.5/day and the interictal EEG showed bilateral, multiregional independent spikes or diffuse spike-and-waves maximal over frontal areas. Ictal onset was not lateralized but dominant at the frontal areas and progressed to rapid generalization. Monopolar bilateral stimulation over ATN was started on both the 1− leads with 1.5 V intensity. Six months after the stimulation, the seizure frequency was definitely reduced to 9.4% of baseline ratio (90.6% reduction).

Patient 6

A 14-year-old female patient with brief, frequent tonic seizures over the trunk and R arm was admitted. Brain MRI showed wide-spread band heterotopia around the lateral ventricles, and interictal and ictal EEG revealed multiregional irritative zones as well as diffuse ictal onset zone. Her seizure frequency was 10–30 per day with predilection of occurrence during morning period. During the seizure, she had usually experienced loss of consciousness for a few to ten seconds, but no secondarily generalized convulsion was found. After ATN electrodes insertion and switch on, she has experienced markedly shortened seizure duration (about 1–2 seconds) and about 50% reduction of seizure frequency for the subsequent 2 months. The long term follow-up should be warranted.

Discussion

Recently, several methods of DBS in refractory epilepsy have been tried and followed in some specialized epilepsy centers. First, the earliest trials were to target crucial structures that are considered as a ‘‘pacemaker’’ or to have an essential role in epileptogenic networks, such as the thalamus or the subthalamic nucleus (‘indirect’ method). Second approach was to interfere with the area

of ictal onset itself (ex. Hippocampus) and prevent the propagation of the seizure ('direct' method). The other method is to deliver the therapeutic electrical stimulation in response to a cue of ictal onset with the use of seizure-detecting or predicting algorithms (Closed-loop systems) [22, 23].

The mechanism of therapeutic action of DBS in reducing seizures remains unclear. But, some different explanations have been proposed. First, DBS may act by blocking local neuronal activity because DBS produces clinical effect similar to that from lesion provoked by the insertion of the electrode itself (microthalamotomy) [11]. A second theory holds that DBS acts through local inhibition induced by current applied to a specific CNS structure. This is the hypothesis of the so-called reversible functional lesion, where in the case of targeting crucial structures in a network, nuclei that are involved in propagating, sustaining, or triggering epileptic activity are inhibited [28]. Our previous paper demonstrated that increased cerebral perfusion areas after STN DBS corresponding to the patient's irritative zones provided a clue to understand the mechanism of DBS in epilepsy [24]. But, in the cases of ATN DBS, similar findings were not shown (not described in this paper). But, the additive results from ongoing functional imaging studies of our patients would provide more convincing answers to solve the problem.

Our patients showed a mean reduction in seizure frequency of 62.3% (49.1% from STN vs. 75.4% from ATN), which are comparable or superior (especially, the results from ATN DBS) to the previous human studies [2, 3, 11, 12]. And it may be oversimplified that the ATN DBS is more suitable than the STN DBS for controlling seizures from partial intractable epilepsy. However, the number of patients treated so far is too small to allow any conclusions.

We had a regretful experience of removal of DBS devices from the accidental wound infection with patient 3, who had shown great improvement of cognitive status and activities of daily living as well as a prominent reduction of seizure frequency. Deep-brain implantation usually is associated with a low incidence of infection ranged from 0 to 10.6% per electrode [4, 10, 13, 21]. The causative organisms most often implicated in DBS hardware infections are staphylococcus, enterobacter, streptococcus, pseudomonas and rarely mycobacterium or candida [21]. Causative bacteria are usually from the patient's skin flora. The other five of our patients have not shown any complications related to hardware or during the DBS parameter change.

Conclusion

In our uncontrolled study of DBS on structures indirectly connected to epileptogenic areas (STN and ATN), we could identify their efficiency and relative safety comparable or superior to previous studies during long-term follow up. Future controlled studies in larger patient series are warranted to increase the knowledge about antiepileptic effects of DBS.

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