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# Vascular changes caused by deep brain stimulation using double-dose gadolinium-enhanced brain MRI

Byeong Sam Choi[1], Yong Hwan Kim[2], Sang Ryong Jeon[3]

1 Department of Neurological Surgery, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea
2 Department of Computer Science and Engineering, University of Notre Dame, Notre Dame, IN, USA
3 Department of Neurological Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

*Corresponding author:*
*Sang Ryong Jeon, M.D., Ph.D., Department of Neurological Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43gil, Songpa-gu, Seoul, Korea, srjeon@amc.seoul.kr.*

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## Abstract

We retrospectively analyzed the clinical data of 32 patients with medically intractable idiopathic Parkinson's disease who had undergone staged bilateral deep brain stimulation of the subthalamic nuclei from January 2007 to May 2011. The vascularture of the patients who received two deep brain stimulations was detected using double-dose gadolinium-enhanced brain MRI. The dimensions of straight sinus, superior sagittal sinus, ipsilateral internal cerebral vein in the thalamic branch and ipsilateral anterior caudate vein were reduced. These findings demonstrate that bilateral deep brain stimulation of the subthalamic nuclei affects cerebral venous blood flow.

*Key Words: nerve regeneration; gadolinium-enhanced brain MRI; deep brain stimulation; subthalamic nuclei; vascularture; straight sinus; superior sagittal sinus; internal cerebral vein in the thalamic branch; anterior caudate vein; KRCF National Agenda Project; neural regeneration*

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## Introduction

Deep brain stimulation has been widely used to treat patients with movement disorders and increasing attention has been paid to its use in the treatment of neurological and psychiatric disorders. However, the influence of subthalamic nucleus or pallidal deep brain stimulation on cerebral vasculature is poorly understood. Even though the metabolic changes caused by deep brain stimulation are being studied using positron emission tomography[1-2], the structural changes in cerebral areas like the intracerebral vasculature have not yet been evaluated[3]. Studies using positron emission tomography or single-photon emission computed tomography have demonstrated that the activity or regional cerebral blood flow in the frontal motor association is known to be increased after deep brain stimulation of the subthalamic nucleus[1-2, 4]. It remains unclear that whether this phenomenon results from improvements in neuronal functionality or activation of subthalamic vasodilator area[5-7].

In this study, we performed a retrospective analysis on vasculature changes caused by deep brain stimulation in patients with medically intractable idiopathic Parkinson's disease using double-dose gadolinium-enhanced brain MRI.

## Results

### MRI follow-up interval

Thirty-two patients who underwent staged bilateral deep brain stimulation of the subthalamic nucleus at Haeundae Paik Hospital, Inje University College of Medicine, Korea were included in this study. The average interval between the first and second preoperative brain MRI scans was 151.5 ± 121.0 days, and 17 patients had an interval of more than 100 days while 15 patients had an interval of less than 100 days. Comparing the first preoperative MRI scan with the second preoperative MRI scan, we did not observe the structural changes such as changes around the subthalamic nucleus or brain atrophy. However, changes in the size of midline venous structure and in a part of ipsilateral venous structures on the first deep brain stimulation side were observed.

A comparison between the first and second preoperative MRI scans showed that the shape of straight sinus was altered in five patients, superior sagittal sinus change was observed in four patients (Figure 1), choroid plexus enhancement was decreased in three patients (Figure 2), and the enhancement of ipsilateral internal cerebral vein in the thalamic branch was decreased in three patients (Figure 3). The dimension of ipsilateral anterior caudate vein was reduced in three patients (Figure 4).

According to the interval between the first and second MRI scans, there was no difference in venous enhancement changes. Among patients who were followed up for less than 100 days, change in straight sinus shape was observed in three patients, superior sagittal sinus change in two patients, no change in choroid plexus enhancement in all included patients, the enhancement of ipsilateral internal cerebral vein in the thalamic branch in two patients, and reduced dimension of ipsilateral anterior caudate vein in one patient. Among patients who were followed up for more than 100 days, straight sinus enhancement was decreased in two

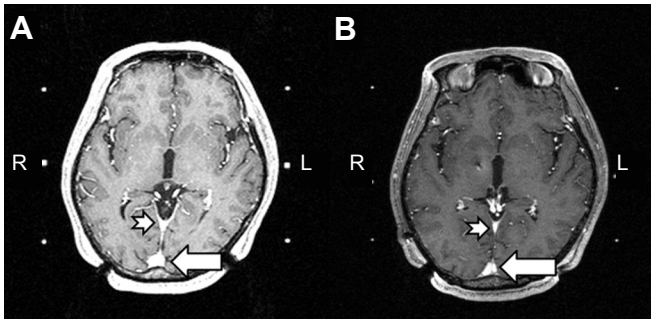


**Figure 1 T1-weighted double-dose gadolinium-enhanced brain MRI scans of a 54-year-old male patient treated with levodopa for 12 years, presenting with aggravated stating hesitancy, turning hesitancy, and whole body dyskinesia.**
A representative brain MRI scan before the first deep brain stimulation of the subthalamic nucleus (STN DBS) (A) and a representative brain MRI scan before the second STN DBS (B) are presented. Dimensions of the straight sinus (indicated by small arrows) and superior sagittal sinus (indicated by large arrows) were calculated using a picture archiving and communication system. R: Right; L: left.

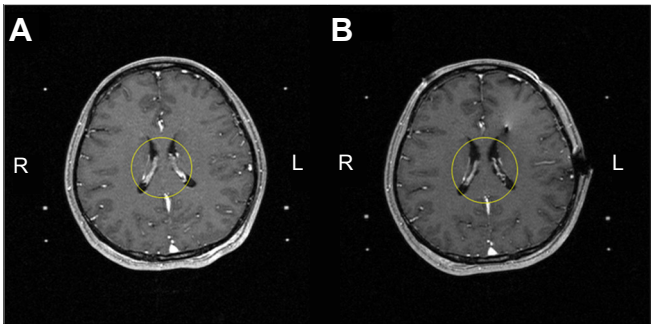


**Figure 2 T1-weighted double-dose gadolinium-enhanced brain MRI scans of a 42-year-old female patient treated with levodopa for 17 years, presenting with aggravated peak dose dyskinesia.**
A representative brain MRI scan before the first deep brain stimulation of the subthalamic nucleus (STN DBS) (A) and a representative brain MRI scan before the second STN DBS (B) are presented. The enhancement of choroid plexus (in circle) shows decrease on the second preoperative brain MRI scan. R: Right; L: left.

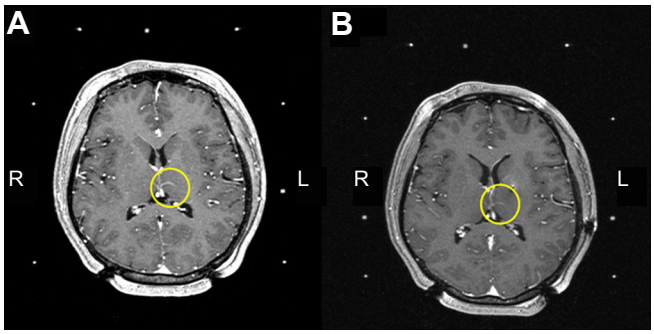


**Figure 3 T1-weighted double-dose gadolinium-enhanced brain MRI scans of a 34-year-old female patient treated with levodopa for 10 years, presenting with aggravated peak dose dyskinesia.**
A representative brain MRI scan before the first deep brain stimulation of the subthalamic nucleus (STN DBS) (A) and a representative brain MRI scan before the second STN DBS (B) are presented. The enhancement of the internal cerebral vein in the thalamic branch (in circle) was found to be decreased on the second preoperative brain MRI scan. R: Right; L: left.

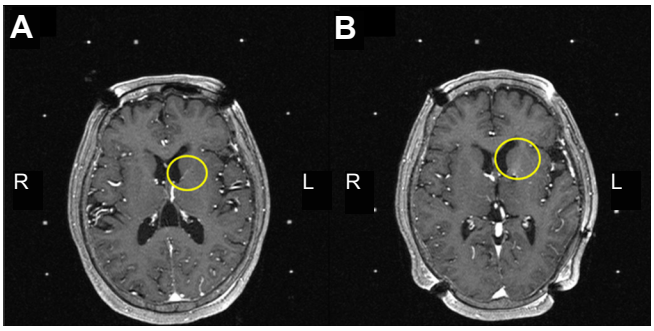


**Figure 4 T1-weighted double-dose gadolinium-enhanced brain MRI scans of a 73-year-old female patient treated with levodopa for 8 years, presenting with aggravated whole body dyskinesia.**
A representative MRI scan before the first deep brain stimulation of the subthalamic nucleus (STN DBS) (A) and a representative MRI scan before the second STN DBS (B) are presented. The enhancement of the ipsilateral anterior caudate vein (in circle) was found to be decreased on the second preoperative brain MRI scan. R: Right; L: left.

patients, superior sagittal sinus change in two patients, decreased choroid plexus enhancement in three patients, decreased enhancement of ipsilateral internal cerebral vein in the thalamic branch in one patient, and reduced dimension of ipsilateral anterior caudate vein in two patients (Table 1).

### Dimensions of the straight sinus and superior sagital sinus

To determine the standardized changes, we calculated the dimensions of the straight sinus and superior sagittal sinus at the anterior commissure-posterior commissure line based on the first and second preoperative MRI scans. The average dimensions of the straight sinus and superior sagittal sinus are shown in Table 2. The dimensions of both midline venous structures were significantly reduced.

All the changes in venous enhancement patterns of MRI were observed on the side of deep brain stimulation even in the choroid plexus except the midline venous structures such as the straight sinus and superior sagittal sinus. There was no change in the enhancement of cortical vessels or vessels around the brain stem (Table 2).

## Discussion

Deep brain stimulation of the subthalamic nucleus has become an established therapeutic approach for the management of patients with advanced idiopathic Parkinson's disease. Results of clinical follow-up studies have shown that deep brain stimulation of the subthalamic nucleus produces a robust improvement in a wide variety of motor symptoms[8] and that this beneficial effect is maintained for several years after deep brain stimulation[9-12]. Despite the fact that these therapeutic benefits are produced over a long period of time, the underlying mechanisms remain unclear[13].

Studies using positron emission tomography or single-photon emission computed tomography have found that deep brain stimulation of the subthalamic nucleus greatly increases movement-related regional cerebral blood flow in the rostral part of presupplementary motor area[1] and improves akinesia over this stimulation period[2, 4].

Several reports, in which animal models were used, suggest that regional cerebral blood flow increases in the fontal area, which occurs possibly owing to activation of the subthalamic vasodilator area by deep brain stimulation of the subthalam

**Table 1 Comparison of enhancement patterns between the first and second preoperative MRI scans**

| Interval of MRI follow up (day) | Straight sinus | SSS | Choroid plexus | Ipsilateral ICV in the thalamic branch | Ipsilateral ACV |
|---|---|---|---|---|---|
| <100 | 3 | 2 | 0 | 2 | 1 |
| ≥100 | 2 | 2 | 3 | 1 | 2 |
| Total | 5/32 | 4/32 | 3/32 | 3/32 | 3/32 |
| *P* value | 0.88 | 0.16 | 0.27 | 0.90 | 0.90 |

SSS: Superior sagittal sinus; ICV: internal cerebral vein; ACV: anterior caudate vein.

**Table 2 Dimensions ($mm^2$) of the straight sinus and superior sagittal sinus (SSS) at the anterior commissure-posterior commissure line**

| | 1st preoperative MRI | 2nd preoperative MRI | *P* value |
|---|---|---|---|
| Straight sinus | 30.2±12.8 | 27.5±10.8 | 0.003 |
| SSS | 50.3±20.0 | 46.0±15.8 | 0.011 |

Data were analyzed using the Fisher's exact test.

ic nucleus[5-7]. On the contrary, a transcranial Doppler study showed that there was no vasodilation change in Parkinson's disease patients who underwent deep brain stimulation of the subthalamic nucleus[3]. Therefore, the mechanism underlying regional cerebral blood flow improvement in motor association area by deep brain stimulation of the subthalamic nucleus is poorly understood. It may be due to activation of subthalamic vasodilator area or improvement in neural functionality. In addition, the presence of anatomical cerebrovascular changes by persistent deep brain stimulation of the subthalamic nucleus is unknown.

In this study, we retrospectively analyzed the changes in enhancement patterns occurring as a result of persistent deep brain stimulation of the subthalamic nucleus using T1 double-dose gadolinium-enhanced brain MRI. The enhanced structures represent vascular structures or condition of perfusion. In this MRI study, we cannot perform arterial phase or venous phase separately, unlike conventional angiography, because it takes long time to make an image. The enhanced MRI with magnetization-prepared rapid gradient-echo technique was used in this study and could display the artery, vein and brain parenchyma simultaneously. However, arterial structure can be distinguished from venous structure by the anatomical location and contrast enhancement in shape on MRI scans. Results from this study reveal a decrease in contrast enhancement of ipsilateral small veins such as internal cerebral vein in the thalamic branch or anterior caudate vein, which suggests the alteration in venous blood flow around the deep brain stimulation electrode. It is likely a simple postoperative change or the effect of persistent electrical stimulation. However, the fact that the sizes of straight sinus and the superior sagittal sinus were reduced significantly implies the global changes of venous flow after deep brain stimulation of the subthalamic nucleus. According to the interval between the first and second preoperative MRI scans, there was no difference in intravenous contrast enhancement changes. Therefore, the duration of electrical stimulation did not affect these changes.

The effect of deep brain stimulation of the subthalamic nucleus on regional cerebral blood flow in the brain stem is controversial. Chronic bilateral deep brain stimulation of the subthalamic nucleus was found to increase bilateral regional cerebral blood flow in the brain stem[4]. Some studies have reported the metabolic decreases in the brain stem after unilateral deep brain stimulation of the subthalamic nucleus or subthalamic nucleus ablation[14-15]. However, we did not observe any change in the venous structure in the brain stem after unilateral deep brain stimulation of the subthalamic nucleus in our study cohort.

The present results regarding changes in the enhancement patterns seem to be opposite to the previous studies which showed increased regional cerebral blood flow by subthalamic nucleus stimulation. However, we believe that the venous structure observed using double-dose gadolinium-enhanced brain MRI does not represent regional cerebral blood flow or metabolism in the brain, and that the effect of deep brain stimulation on brain metabolism is not well understood.

In conclusion, the changes in venous enhancement patterns in a minority of cases and the decreased dimensions of the straight sinus and superior sagittal sinus after unilateral deep brain stimulation of the subthalamic nucleus were observed on brain MRI scans in this study, which cannot be explained by previous brain metabolism findings. Further studies are needed to evaluate the effects of deep brain stimulation on cerebral vasculature.

## Subjects and Methods

### Patient characteristics

We retrospectively reviewed 32 patients with medically intractable idiopathic Parkinson's disease who had undergone staged bilateral deep brain stimulation of the subthalamic nucleus from January 2007 to May 2011. Bilateral deep brain stimulation of the subthalamic nucleus was performed only when medical therapy was failed, including (1) severe motor fluctuations; (2) severe dyskinesia; (3) tremor uncontrollable by medications; (4) painful dystonia; (5) side effect for medication (drug-induced psychosis, nausea, vomitting). Dementia, cognitive deficits and psychosis (not drug-induced) were not included in surgical indications. The mean patient age at the time of deep brain stimulation was 54.3 years (range, 34–73 years). The first and second deep brain stimulation manipulations were separated by an average of 151 days (range, 56–474 days).

The indication for deep brain stimulation was medically intractable motor fluctuation or levodopa-induced dyskinesia. The first deep brain stimulation was performed con-

tralateral to the more symptomatic side of the body. When a patient demonstrated symmetrical distribution of Parkinsonian features, we selected the dominant side of the brain for the first deep brain stimulation. The second deep brain stimulation was performed when the patient was fully recovered from the first deep brain stimulation and desired a second operation.

## Methods

### *Procedures*

The neurosurgical procedures were performed by the same surgeon Dr. Jeon who had performed 500 times or more deep brain stimulations during 10 years. All patients were prepared for deep brain stimulation using the same method described by Park et al.[16]. We did not perform bilateral deep brain stimulations at the same time.

The first deep brain stimulation was performed contralateral to the more symptomatic side of the body and the other side was done after about 3 month later. MRI scan was performed at approximately the same time (7:00–8:00 a.m.). Briefly, the patient was placed in a sitting position and a stereotactic head frame (Leksell model G, Elekta Instruments, Stockholm, Sweden) was affixed to the patient's head after local administration of 1% lidocaine. The MRI (Magnetom Avanto, Simens, Munich, Germany) was performed using the same machine in each case (1.5T). Double-dose gadolinium-enhanced whole brain MRI (slices, 160; repetition time/echo time, 1,870.0/3.6; slice thickness, 1.0 mm) with magnetization prepared rapid gradient echo technique was performed to show the artery, vein, and brain parenchyma simultaneously. We planned the electrode insertion trajectory using double-dose gadolinium-enhanced whole brain MRI. The gadolinium dose was 0.2 mmol/kg and the imaging was performed immediately after cephalic vein or median cubital vein injection. Imaging data were transferred to a Surgiplan (Elekta, Stockholm, Sweden) system to determine the optimal target based on known anatomical coordinates. For the second deep brain stimulation, the same method and MRI technique were applied.

To evaluate the changes in the vasculature or other structures, we compared T1-weighted axial preoperative gadolinium-enhanced brain MRI results before the first deep brain stimulation with the preoperative MRI data obtained before the second deep brain stimulation. The images were adjusted through the anterior commissure-posterior commissure line and the dimensions of the straight sinus and superior sagittal sinus were calculated by a picture archiving and communication system (Maroview; Marotech, Seoul, Korea) (Figure 1). A statistical comparison was performed using the Fisher's exact test and paired *t* test (IBM SPSS statistic software; SPSS Korea Data Solution Inc., Seoul, Korea). The significance level was set at $P = 0.05$ for all analyses.

### *Deep brain stimulation procedure*

After deep brain stimulation of the subthalamic nucleus, the stimulation started at postoperative 14$^{th}$ day when the insertion site of electrode (Medtronic, Minneapolis, MN, USA) in the brain was stabilized. The stimulation parameters were voltage range 0.5–5.0 V, pulse width range 60–90 s, and frequency range 60–185 Hz.

**Author contributions:** *Choi BS performed experiments and wrote this paper. Kim YH analyzed experimental data. Jeon SR designed this study and supervised all experiments. All authors approved the final version of this paper.*
**Conflicts of interest:** *None declared.*

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