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CLINICAL ARTICLE

The Influence of Calvarial Thickening in Epilepsy Patients on Deep Brain Stimulation

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Objective: Deep brain stimulation (DBS) has been applied on the wide range of movement disorders. Recently, application of DBS to epilepsy has shown an acceptable outcome. In epilepsy patients, calvarial thickening is a well-known phenomenon. This phenomenon is a bothersome point in conducting DBS surgery due to its technical difficulty to drill a burr hole in the precise coaxial trajectory of the DBS lead and it often requires additional drilling. In this study we focus on the skull thickness of epilepsy patients, compared it to movement disorder patients to prognosticate technical difficulties of DBS on epilepsy patients.
Methods: 21 patients who underwent DBS surgery from Nov. 2017 to Sep. 2018 in Samsung Medical Center were included. Direct measurement during operation with a Vernier caliper was used to obtain each individual patient's skull thickness. Patients were divided into two subgroups depending on the patient's disease entity. SPSS was used for statistical data analysis.
Results: Six epilepsy patients and 15 movement disorder patients were identified. The contrast of patient-related factors between two groups was not significant, except for skull thickness. The skull of the epilepsy patient group were significantly thicker than in the movement disorder patient group ($p=0.049$). Skull thickness was not affected by sex and age. The mean difference of skull thickness between the epilepsy and movement disorder group was 0.3cm. In the epilepsy patient group, there was a tendency in which the skull thickness increases in patients with longer duration of antiepileptic drug (AED) use.
Conclusions: Calvarial thickening is a known phenomenon frequently observed in epilepsy patients. Therefore, when DBS is performed in epilepsy patients, a thick skull should be considered prior to surgery to avoid additional surgical complications.

KEY WORDS: Deep brain stimulation · Skull thickness · Epilepsy.

INTRODUCTION

The applicable disease entity of deep brain stimulation (DBS) has been widened since the start of the modern era of DBS 30 years ago. Nowadays, application of DBS to epilepsy has been attempted and many authors have reported successful outcomes.[3)10)] For DBS, the burr hole method is generally preferred in which a burr hole is made in a coaxial trajectory of the DBS lead. However, trephination of the skull is generally performed using a non-stereotactic technique, often leading to technical errors such as DBS lead trajectories not fitting in the initial burr hole.[9)] In such case, additional drilling is required to enlarge the burr hole, and this procedure is often time consuming and moreover invasive leading to post-operative complication such as epidural hematomas, cerebrospinal fluid leakage and intracranial air collection.[11)] Patient factors such as skull thickness is also related in such manner since the allowable range of trajectory in which the microelectrode safely passes through the outer and inner cortex without hitting the edge of the patient's skull is directly influenced by skull thickness. Lately, non-invasive neurosurgical procedure such as magnetic resonance-guided focused ultrasonography (MRgFUS) has been introduced which is also highly affected by skull thickness.[1)] From the facts above, we focused on the importance of skull thickness and its differences upon diseases. There are many reports which epilepsy patients has thick skull because of the effects of antiepileptic drugs.[4)8)] In this study, we direct measured the skull thickness of patients who underwent DBS surgery at the Kocher's point, and investigated the differences between epilepsy patients and movement disorder patients. This is in our best knowledge the first report directly measuring skull thickness and related it to a disease entity.

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MATERIALS AND METHODS

This study included patients who underwent DBS surgery from Nov. 2017 to Sep. 2018 in Samsung Medical Center. The electronic medical records of 43 patients were reviewed retrospectively. Each patient's disease entity, age, sex and skull thickness were thoroughly assessed. Among 43 patients, 22 patients were excluded due to absence of skull thickness data. Patients were divided into 2 groups of epilepsy and movement disorder. The movement disorder group includes dystonia, essential tremor and Parkinson's disease. The skull thickness of each patient was directly measured during operation. After burr hole trephination, the depth of the outer skull cortex to dura was measured using a Vernier caliper. For bilateral burr hole patients, the mean skull thickness was used for data analysis. Continuous variables were reported with means and ranges. Categorical variables were expressed as frequencies. Contrast between patient-related factors in DBS patients by disease entity were analyzed by Fisher's Exact Test, independent t-test, and Mann-Whitney test. Correlation between skull thickness and patient related factors were analyzed by Spearman's rho test, independent t-test, and Mann-Whitney test. $P \leq 0.05$ was considered statistically significant throughout all statistics. All statistical analysis was performed using the SPSS Statistics (IBM, Chicago, IL, USA).

RESULTS

This study consisted of 21 patients. All patients were divided into two categories by disease entity. Six patients had been diagnosed as epilepsy. The others had been diagnosed as movement disorder. In detail, the movement disorder group consist of 1 dystonia, 3 essential tremor and 11 Parkinson's disease patients. The Demographic characteristics of each group are summarized in Table 1. The patients included fourteen women and seven men with a mean age of 53.3 (range : 24–74 years). The mean skull thickness was 0.87cm (Range : 0.54–1.80cm). Depending on the disease entity, patient's sex did not show significant difference. Epilepsy patients were younger than movement disorder patients (p=0.001) and the skull thickness was greater in epilepsy patients (p=0.049).

Table 1. Demographic characteristics of each group

	Epilepsy	Movement disorders	p value
Number of cases	6	15	N/A
Sex (M:F)	3:3	4:11	0.299
Age (years)	32.7 (24–42)	61.6 (39–74)	0.001
Skull thickness (cm)	1.09 (0.54–1.80)	0.79 (0.60–1.05)	0.049

∗ : Values are presented as the mean (range), † : Boldface indicates a significant correlation (p<0.05). N/A : not applicable

The correlation between skull thickness and each patient related factor is summarized in Table 2. Among them, patient's disease entity was the only factor related with skull thickness (p=0.049). The mean difference of skull thickness between two disease entity was 0.3cm. As seen in Fig. 1, although the range of skull thickness in epilepsy patients was broad, the mean skull thickness was significantly greater in epilepsy patients.

The clinical characteristics of epilepsy patients are summarized in Table 3. The median age was 31 years old (range : 26–42). Male and female patients were same as 3 patients. The median duration of antiepileptic drugs (AED) use was 159.5 months (range : 28–318). AEDs such as Topiramate and Valproate were commonly used, which used in 4 patients. Generalized tonic-clonic seizure was the most common semiology. The duration of AED use and skull thickness tended to have a positive relationship. However, statistical

Table 2. Correlation between skull thickness and each patient related factor

Factor	Disease	Sex	Age
Skull thickness	p=0.049*†	p=0.743‡	p=0.324§

∗ : Significant correlation (p<0.05), † : Independent t-test, ‡ : Mann-Whitney Test, § : Spearman's rho test

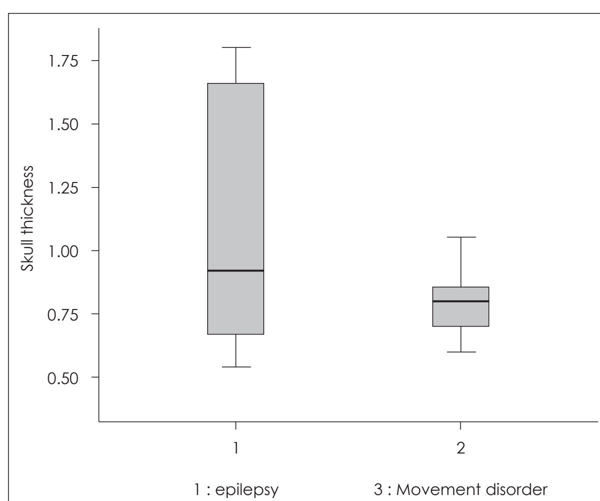

Fig. 1. Skull thickness depends on disease entity. The range of skull thickness in epilepsy patients was broader and the mean skull thickness of epilepsy patients was significantly greater than movement disorder patients.

Table 3. The clinical characteristics of epilepsy patients

Patients	Age	Sex	Diagnosis	Semiology	Duration of AED use (months)	Kinds of used AED	Skull thickness (cm)
1	36	M	Localization-related symptomatic epilepsy with intractable epilepsy	GTC	28	Lacosamide Levetiracetam Lamotrigine Topiramate Valproate	0.54cm
2	42	F	Localization-related symptomatic epilepsy with intractable epilepsy	Gelastic Automotor	225	Carbamazepin Clobazam Lacosamide Levetiracetam Lamotrigine	0.88cm
3	24	F	Localization-related symptomatic epilepsy with intractable epilepsy	Atonic	81	Oxcarbazepine Clobazam Lamotrigine Topiramate	0.67cm
4	26	M	Unspecified epilepsy without intractable epilepsy	Automotor	318	Clobazam Clonazepam Topiramate Valproate	1.66cm
5	42	M	Unspecified epilepsy without intractable epilepsy	GTC	94	Clobazam Valproate	0.96cm
6	26	F	Localization-related symptomatic epilepsy with intractable epilepsy	GTC	257	Carbamazepin Lacosamide Levetiracetam Topiramate Valproate	1.8cm

AED : antiepileptic drug, GTC : generalized tonic-clonic

analysis was not possible due to small sample size.

Case illustration

Case 1 : Epilepsy patient

A 26-year-old man with epilepsy had a bilateral centromedian (CM)-DBS performed. Burr holes were made at the bilateral Kocher's point using a Midas Rex perforator with a 14mm perforator bit (Medtronic Inc., Minneapolis, Minnesota, USA). His skull thickness was directly measured using a Vernier caliper. The thicknesses of his skull in the right and left burr hole were 1.55cm and 1.76cm, respectively. The mean skull thickness was 1.66cm which was considered very thick in our study. When inserting a microelectrode, we encountered technical difficulty in which the microelectrode was not able to enter the preplanned target lesion through the planned trajectory without hitting the edge of the internal cortical bone. Therefore additional drilling to make the burr hole wider or rearrangement of entry point was required. We decided to change the entry point and insertion angle to complete the procedure. A postoperative CT scan was performed and a 3 dimension reconstruction was obtained using materialise 3-matic (Materialise Software, Leuven, Belgium). Fig. 2 demonstrates the reconstructed skull of the patient. Left

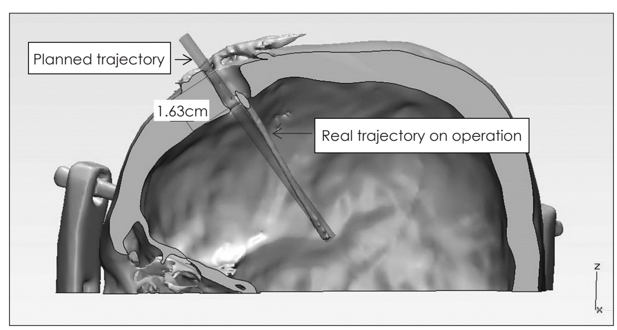

Fig. 2. The illustrated case 1 : 3D reconstructed skull of epilepsy patient who is a 26-year-old man and underwent bilateral centromedian (CM)-DBS. Left cylinder represented a pre-planned trajectory and right cylinder represented a new trajectory which is an actual trajectory in operation.

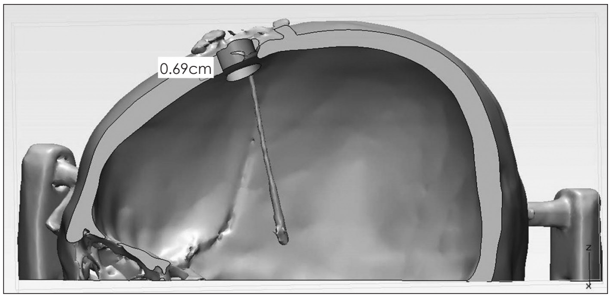

Fig. 3. The illustrated case 2 : 3D reconstructed skull of Parkinson's disease patient who is a 51-year-old man and underwent bilateral subthalamic nucleus (STN)-DBS. A cylinder represented a pre-planned trajectory which is same as an actual trajectory in operation.

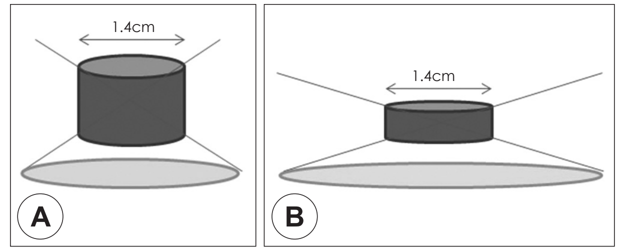

Fig. 4. The schematic illustration of surgical trajectory according to skull thickness. A : A schematic view of skull in epilepsy patient group. B : Schematic view of skull in movement disorder patient group. In both schematic views, the maximum ranges of entry angle and reachable target space using same burr hole were drawn as inverted cone and cone. Epilepsy patient group shows much smaller range of entry angle and reachable target space.

cylinder represented planned trajectory and right cylinder represented actual trajectory in operation. The measured skull thickness in the 3D model was 1.63cm and this was slightly different from the directly measured skull thickness.

Case 2 : Movement disorder patient

Bilateral subthalamic nucleus (STN)-DBS was performed to a 51-year-old man diagnosed with Parkinson's disease. Burr holes were made at the bilateral Kocher's point using a Midas Rex perforator with a 14mm perforator bit (Medtronic Inc., Minneapolis, Minnesota, USA). His skull thickness was directly measured using a Vernier caliper. The skull thicknesses of both sides were identical of 0.6cm. Insertion of the microelectrode was performed without any technical difficulty and therefore not requiring additional drilling or alteration of entry point. A postoperative CT scan was performed and 3 dimension reconstruction was obtained using materialise 3-matic (Materialise Software, Leuven, Belgium). Fig. 3 demonstrates the reconstructed skull of the patient. The measured skull thickness in the 3D model was 0.7cm which was slightly different from the directly measured skull thickness.

DISCUSSION

The calvarial thickening in epilepsy patients has been reported previously.[4)6)8)] However, to our knowledge, direct measurement of skull thickness in epilepsy patients has not been attempted in the past.

In this study, the epilepsy patient group seems to have a relatively thick skull compared to the movement disorder patient group (Table 1). The reason of calvarial thickening in epilepsy patients are known for its association with AED. The drug which most commonly induces calvarial thickening is phenytoin.[4)6)] The upregulation of the transforming growth factor-beta1 and bone morphogenic proteins, which in turn increase osteoblast proliferation has been suggested as the pathological mechanism of action.[2)] Siddiqui and Singh have reported that AED other than phenytoin can also be associated with calvarial thickening.[8)] Further evaluation is needed to determine which AED is associated with calvarial thickening in our study. There is a possibility that the duration of AED use has a positive relationship with skull thickness therefore needs further evaluation with a larger number of patients.

The calvarial thickening phenomenon brings a bothersome point to DBS. When epilepsy patients with thick skulls undergo DBS, a slight deviation of the burr hole from the planned trajectory in the external cortical bone may become a large deviation in the internal cortical bone. In such a case, when the microelectrode is placed in the external cortical bone of the burr hole, the tip of the microelectrode may hit the edge of the internal cortical bone of the burr hole making it impossible to pass through. Also adjustable intracranial space in epilepsy patients is smaller than in movement disorder patients. Fig. 4 shows two schematic illustrations of a patient's skull with 14mm burr hole. Case 1 is a schematic view of skull in an epilepsy patient group and case 2 is a schematic view of skull in a movement disorder patient group. When the microelectrode passes through the bony cranium, the maximum range of angle not conflicting the bony edge from the entry point to the target point was drawn as cone and inverted cone. Supposing the depth to the coaxial target is identical in both cases the diameter of the cone was clearly smaller in the epilepsy patient group. The schematic view of the epilepsy patient group showed a much smaller range of angle at entry and reachable target space than in the movement disorder patient group. In these circumstances, the epilepsy patient group may require additional drilling to enlarge the burr hole which increases possibility of post-operative complication such as cerebrospinal fluid (CSF) loss and intracranial air collection. These intracranial changes may induce structural dislocation of the brain parenchyme which is an unfavorable factor for precise DBS lead placement.[5)7)]

Another point which is interesting is the difference of skull thickness between CT scan measurement and manual intraoperative measurement. As seen in the illustrated case above. The thickness of the skull could be different depending on the measurement method. When we directly measured the patient's skull thickness intraoperatively, measurement was conducted from entry point of dura to outer skull cortex vertically. However, when we measured the skull thickness on CT scan, measurement was conducted near the burr hole site on a sagittal plane. In this case, there is possibility that the skull thickness may not be vertically measured due to the fact that the sagittal CT image may be slightly tilted from the true sagittal plane. In the near future, the exact difference of skull thickness between the two measurement methods will be needed to evaluate.

From the results of our study, we suggest the burr hole should be larger than ordinary or be located with a stereotactic technique when performing DBS for epilepsy patients. The stereotactic burr hole technique for DBS was introduced and have shown effectiveness to avoid additional drilling which can lead to post-operative complications.[9)]

CONCLUSION

Calvarial thickening is a known phenomenon frequently observed in epilepsy patients due to AED medication. Therefore, when DBS is considered for epilepsy, precise entry point targeting with stereotactic technique or implementing a larger size burr hole is needed to obtain maximal effect of DBS and to prevent surgical complication.

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