Calvarial Thickening in Tuberous Sclerosis Complex

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BACKGROUND: **Tuberous sclerosis complex (TSC)–related skeletal abnormalities are understudied. Awareness of skull thickening in patients with TSC is important from the surgical standpoint because a thick skull might complicate craniotomy. This study aimed to discover if patients with TSC are generally prone to skull thickening by retrospectively investigating the frequency and characteristics of skull thickening in these patients.**

METHODS: **Patients with TSC ages 10 to 60 years who underwent magnetic resonance imaging in the neurosurgery, dermatology, or pediatrics clinic between 2010 and 2021 were identified. Two control groups were used for comparison: one with patients with unruptured intracranial aneurysms to serve as control without antiseizure medication exposure and one with non-TSC epilepsy as control with antiseizure medication exposure. In all patients, thickness of frontal, parietal, temporal, and occipital bones was measured at a fixed location of each bone on T2-weighted axial images.**

RESULTS: **Inclusion criteria were fulfilled by 29 patients. Frontal and temporal bones of the TSC group were significantly thicker than those of either control group. Skull thickening was significantly associated with intracerebral calcification, but not with age, sex, or antiseizure medication exposure. Focal skull thickening was associated with the presence of a subcortical calcification.**

CONCLUSIONS: **Patients with TSC have skull thickening, which is often linked to intracerebral calcification. The presence of skull thickening may require modification of surgical approach during craniotomy. Skull thickening and the underlying intracerebral calcification likely share a common precipitating factor given their relationship. Future studies are warranted to clarify the genetic underpinnings of this relationship and even broader skeletal abnormalities in TSC.**

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal genetic disorder caused by pathological variants in either the *TSC1* or the *TSC2* gene, which results in the dysfunction of hamartin and tuberin complex and disinhibition of mTORC1 protein. This forms the basis for the characteristic benign tumor growth in various systems of patients with TSC, including renal angiomyolipoma, lymphangioleiomyomatosis, facial angiofibromas, subcortical tubers, and subependymal giant cell astrocytoma in the brain.[1] Epilepsy is a common manifestation of TSC that often manifests during childhood. Epilepsy may cause neurological regression in young children and impact social functioning in adults, especially in patients who develop drug resistance.[2,3] Surgery is recommended in such cases.[4]

Before the present study, we encountered a patient with TSC in whom we found an unusual skull thickening during craniotomy for epileptic focus resection. This focal thickening of the squamous bone overlaid a calcified subcortical tuber. The focal skull thickening and the calcified tuber were characterized by their unique interlocking shapes, which suggested a possible

Key words
- Craniotomy
- Skull thickening
- Tuberous sclerosis complex

Abbreviations and Acronyms
ASM: Antiseizure medication
AC-PC: Anterior commissure — posterior commissure
CT: Computed tomography
MRI: Magnetic resonance imaging
NE: Non-epilepsy
TSC: Tuberous sclerosis complex

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association between skull thickening and intracerebral calcification.

Skeletal lesions including skull lesions have been documented in patients with TSC.[5,6] However, these skeletal abnormalities are considered less important in the diagnosis of TSC[7] and thus have been studied less. Skull thickening in TSC was reported as patches of increased bone density of the skull, likely associated with the underlying tuber, in the radiographic era before computed tomography (CT) and magnetic resonance imaging (MRI) were widely available.[8] However, it has received little attention since the widespread use of these modern imaging modalities, and thus details regarding skull thickening in TSC, including its prevalence, remain scarce. Meanwhile, as mTORC1 protein abnormalities are reported to be associated with abnormalities in skeletal development,[5,6,9] skull thickening may occur in patients with TSC.

We wondered if patients with TSC are prone to skull thickening in general and, if so, whether the thickening was related to the presence of calcified subcortical tubers. To answer these questions, we performed a retrospective study in a cohort of patients with TSC treated at our hospital. It is hoped that the findings of this study will enhance the awareness of skull thickening, which might influence preoperative planning or surgical approach when craniotomy for epilepsy surgery is considered in TSC.

MATERIALS AND METHODS

All patients between 10 and 60 years of age with a diagnosis of TSC who were managed at the neurosurgery, dermatology, or pediatrics clinic and underwent head MRI at our hospital between January 2010 and January 2021 were included in this study. We opted to use MRI instead of CT because head CT was rarely performed for clinical purposes in these patients at our hospital. We did not perform head CT for the purpose of this study due to its retrospective nature. MRI were chosen clinically because it poses no risk of exposure to radiation and is optimal for screening and follow-up of intracranial lesions. The present study was approved by the Ethics Committee of Osaka University Hospital, and all patients gave their consent through an opt-out policy.

To evaluate if patients with TSC have thicker skulls in general, we used a group of patients with unruptured intracranial aneurysms considered to be the closest to the healthy population to serve as a control non-epilepsy (NE) group. The NE group comprised an equal number of consecutive patients between 10 and 60 years of age who underwent neuroangiography between May 2019 and January 2021. Because TSC is associated with epilepsy, some patients were likely exposed to antiseizure medications (ASMs) that might affect bone thickness.[10-12] Thus, we used a second group of patients with epilepsy not related to TSC to serve as a control group that represented the population with ASM exposure. The epilepsy group comprised an equal number of patients 10 to 60 years of age from a database of patients who underwent video electroencephalography and received head MRI scans during the same time period as the TSC group. These patients were selected to represent a population with age and imaging protocol as similar as possible to the patients with TSC (Figure 1).

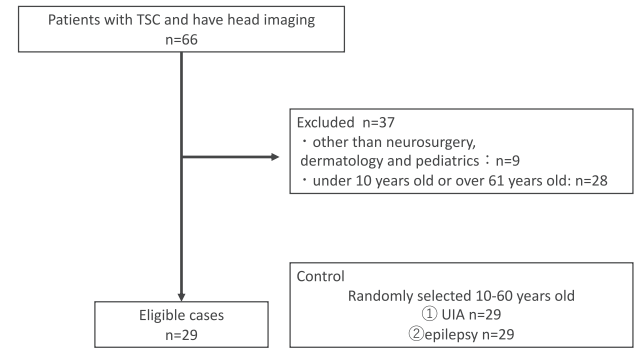

Figure 1. Patient selection. TSC, tuberous sclerosis complex; UIA, unruptured intracranial aneurysm.

We extracted demographic data including sex, age, and ASMs taken at the time of head imaging from the medical record. We visually reviewed the MRI of each patient to detect the presence of an intracerebral calcification measuring >5 mm, to measure the bone thickness, and to localize skull thickening in relation to the calcification. Intracerebral calcifications detected were either calcified subcortical tubers or calcified subependymal nodules.

We measured the respective thickness of the frontal, parietal, temporal, and occipital bones on MRI T2-weighted axial images of each patient. MRI slice thicknesses were 3 or 5 mm. As axial images were acquired parallel to the anterior commissure–posterior commissure (AC-PC) plane, each bone was measured at a fixed location on a slice with a fixed distance from the AC-PC plane to maximize the uniformity of measurement for all patients. The frontal bone was measured at a point located 24–25 mm superior to the AC-PC plane and 20 mm lateral from midline; the parietal bone was measured at a point located 30 mm superior to the AC-PC plane and the furthest from midline; the temporal bone was measured at a point located 24–25 mm inferior to the AC-PC plane on a line perpendicular to the AC-PC plane and traversing the basilar artery; the occipital bone was measured at a point located at same plane as the temporal bone and 20 mm lateral from midline. Thickness, defined as the distance between the inner and outer table (both appeared as a low-intensity layer beneath the scalp on T2-weighted MRI), was measured on a line perpendicular to each bone at the points as mentioned above.

For each bone, thickening was considered present if the bone thickness was greater than or equal to the 98th percentile bone thickness of the NE control groups. In addition, a circumscribed thickening by >1.4 times compared with the contralateral on the same site was defined as focal skull thickening or otherwise as diffuse skull thickening. These cutoffs were defined arbitrarily due to the lack of prior similar study. To explore if patients with TSC were prone to skull thickening, the difference between TSC and each control group in the thickness of each bone was analyzed. To explore the effect of age, sex, ASMs, phenytoin, and the presence of intracerebral calcification on skull thickening, the difference in each factor between patients with TSC with and without skull thickening was analyzed.

Table 1. Patient Characteristics and Thickness of Each Cranial Bone

	TSC Group (n = 29)	Control 1 (Non-epilepsy) Group (n = 29)	P Value*	Control 2 (Epilepsy) Group (n = 29)	P Value*
Age, median (0%—100%)	15 (10—44)	49 (32—60)	<0.01	16 (10—41)	0.89
Sex, male, %	65.5	27.6	<0.01	62.1	0.78
Number of ASMs, median (0%—100%)	1 (0—5)	0	<0.01	2 (1—5)	<0.01
Patients taking phenytoin, %	13.8	0	0.11	3.4	0.35
Thickness of frontal bone, mm, median (10%—90%)	6.05 (3.13—9.33)	4.4 (2.56—5.95)	—	3.76 (2.37—5.77)	—
Thickness of parietal bone, mm, median (10%—90%)	5.11 (3.04—7.30)	4.31 (2.89—5.59)	—	3.42 (2.28—4.64)	—
Thickness of occipital bone, mm, median (10%—90%)	4.78 (3.38—6.29)	5.27 (3.34—6.32)	—	3.71 (2.13—6.41)	—
Thickness of temporal bone, mm, median (10%—90%)	3.85 (1.96—7.67)	2.54 (1.71—4.31)	—	2.45 (1.51—4.84)	—

TSC, tuberous sclerosis complex; ASM, antiseizure medication.
*Indicates Steel test P value when comparing the TSC group with either control group.

Statistical Analysis

Statistical analyses were performed using JMP software version 16.0 (SAS Institute Inc., Cary, North Carolina, USA). We used Mann-Whitney U test to test the difference between 2 continuous or ordinal variables and χ^2 test or Fisher exact test to test the difference between categorical variables. Steel test was used when comparing the TSC group with either control group. We opted for a nonparametric test because of the small sample size. P value < 0.05 was considered significant.

RESULTS

Patient Characteristics

The inclusion criteria were fulfilled by 29 patients with TSC. The TSC group was between ages 10 and 44 (median 15 years old) and taking a median of 1 ASM. The NE group was between ages 32 and 60 (median 49 years old). The epilepsy group was between ages 10 and 41 (median 16 years old) and taking a median of 2 ASMs. There was no significant difference between the TSC group and

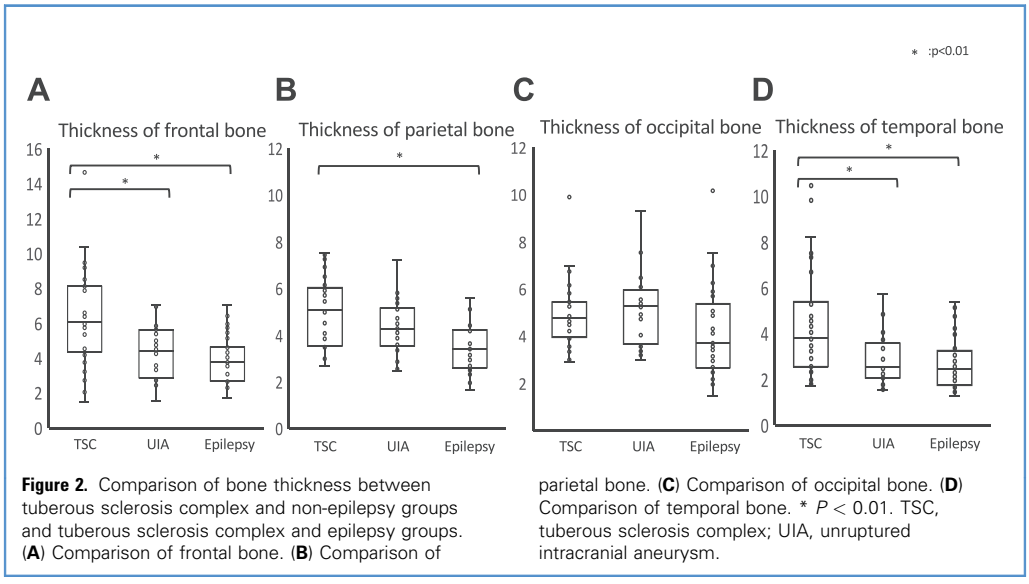

Figure 2. Comparison of bone thickness between tuberous sclerosis complex and non-epilepsy groups and tuberous sclerosis complex and epilepsy groups. (**A**) Comparison of frontal bone. (**B**) Comparison of parietal bone. (**C**) Comparison of occipital bone. (**D**) Comparison of temporal bone. * $P < 0.01$. TSC, tuberous sclerosis complex; UIA, unruptured intracranial aneurysm.

Table 2. Characteristics of Patients with Skull Thickening

Patient No.	Age (years)/ Sex	Type of Skull Thickening	Right Frontal Bone (mm)	Left Frontal Bone (mm)	Right Parietal Bone (mm)	Left Parietal Bone (mm)	Right Occipital Bone (mm)	Left Occipital Bone (mm)	Right Temporal Bone (mm)	Left Temporal Bone (mm)	ASMs	Phenytoin	Cortical Calcification	Location of Calcification
1	30/male	Focal	6.59	7	3.72	3.29	4.75	4.68	6.12	13.56	0	–	+	Surface (left temporal)
2	10/male	Focal	8.63	8.42	5.24	9.29	3.36	2.66	2.98	3.53	2	–	+	Surface (left frontal + parietal)
3	14/male	Diffuse	5.34	6.57	5.83	5.61	10.54	9.28	3.89	3.07	2	–	+	Deep
4	17/male	Focal	8.26	10.09	4.06	5.94	3.66	3.66	2.21	3.66	1	–	+	Deep
5	18/female	Diffuse	16.55	12.76	6.8	7.08	4.84	4.46	8.05	7.01	1	–	–	—
6	23/female	Diffuse	6.78	9.43	5.84	6.06	5.53	5.48	6.09	4.5	5	+	+	Deep
7	31/female	Diffuse	6.42	6.33	4.25	4.04	2.79	4.34	6.65	8.02	1	–	–	—
8	15/male	Diffuse	6.27	6.78	6.54	6.52	6.79	6.72	4.22	3.33	0	–	–	—
9	39/female	Diffuse	9.16	9.43	8.74	6.32	4.77	4.54	6.36	7.06	0	–	–	—
10	11/male	Focal	8.88	7.45	3.3	3.8	6.6	4.34	6.91	3.88	3	+	–	—
11	12/male	Focal	9.27	9.65	8.63	6.29	4.52	4.45	6.49	4.42	3	–	+	Surface (right parietal)
12	22/male	Focal	6.58	9.15	7	7.95	2.94	6.62	7.91	13.04	0	–	+	Surface (right parietal)
13	42/female	Focal	9.21	11.5	4.43	7.45	3.44	3.33	7	9.5	4	+	–	—

ASM, antiseizure medication.

Table 3. Comparison of Age, Sex, Presence of Calcification, and Presence of Antiseizure Medications in Tuberous Sclerosis Complex Patients with and without Skull Thickening

	Skull Thickening ($n = 13$)	No Skull Thickening ($n = 16$)	*P* Value
Age, years, median	18	14.5	0.21
Presence of intracerebral calcification, number (%)	7 (53.8)	1 (6.3)	<0.01
Male, number (%)	8 (61.5)	11 (68.8)	0.68
Taking ASMs, number (%)	9 (69.2)	8 (50)	0.30
Taking phenytoin, number (%)	3 (23.1)	1 (6.3)	0.30

ASM, antiseizure medication.

the epilepsy group in the number of patients taking phenytoin (P = 0.35) (Table 1).

Skull Thickness of Patients with TSC

Patients in the TSC group had significantly thicker frontal and temporal bones, but not occipital bones, compared with either control group (Figure 2). The median thickness of the frontal bone was 6.05 mm in the TSC group, 4.40 mm in the NE group (P < 0.01), and 3.76 mm in the epilepsy group (P < 0.01). The median thickness of the parietal bone was 5.11 mm in the TSC group, 4.31 mm in the NE group, and 3.42 mm in the epilepsy group (P < 0.01). The median thickness of the occipital bone was 4.78 mm in the TSC group, 5.27 mm in the NE group, and 3.71 mm in the epilepsy group. The median thickness of the temporal bone was 3.85 mm in the TSC group, 2.54 mm in the NE group (P < 0.01), and 2.45 mm in the epilepsy group (P < 0.01) (Table 1).

Skull Thickening in Patients with TSC

The cutoff thickness in defining skull thickening (see above—bone thickness greater than or equal to the 98th percentile bone thickness of the NE control groups) was 7.00 mm for the frontal bone, 6.43 mm for the parietal bone, 8.32 mm for the occipital bone, and 5.06 mm for the temporal bone. Among the 29 patients in the TSC group, skull thickening was found in at least one among the frontal, parietal, occipital, and temporal bones in 13 patients; thickening of the frontal bone was found in 10 patients. Diffuse skull thickening was seen in 6 patients, and focal skull thickening was seen in 7 patients (Table 2).

The presence of intracerebral calcification was significantly associated with skull thickening, whereas age, sex, and presence of ASMs were not. In addition, focal skull thickening was associated with the presence of a superficial calcification (Tables 3 and 4).

Illustrative Cases

Case 1 (Patient 1): Focal Skull Thickening. A 30-year-old man had drug-resistant epilepsy related to TSC. He had a superficial calcified subcortical tuber in the left temporal lobe that was associated with focal skull thickening of the inner table of the temporal bone in the vicinity (Figure 3). He underwent epileptic focus resection of the left temporal lobe following stereoelectroencephalography. Due to the skull thickening, the temporal craniotomy required some extra steps, including drilling off the protruded inner table.

Case 2 (Patient 5): Diffuse Skull Thickening. A 18-yearold women had epilepsy related to TSC. She had diffuse skull thickening in the frontal bone without an underlying calcified subcortical tuber (Figure 3). Her epilepsy was well controlled with 1 ASM.

DISCUSSION

In this study, we showed that patients with tuberous sclerosis have thicker frontal and temporal bones compared with control groups and that focal skull thickening is associated with the presence of superficial intracerebral calcification in the vicinity. Significant thickening was observed in the frontal and temporal bones of the TSC group compared with either control group. While ASMs are known to cause skull thickening,[10-12] bones were thicker in the

Table 4. Comparison of Location of Intracerebral Calcified Lesions and Type of Skull Thickening in Tuberous Sclerosis Complex Patients with Skull Thickening

Location of Intracerebral Calcified Lesion	Focal Skull Thickening ($n = 7$)	Diffuse Skull Thickening ($n = 6$)	*P* Value
Superficial, number (%)	4 (57.1)	0 (0)	0.01
Deep, number (%)	1 (14.3)	2 (33.3)	0.41

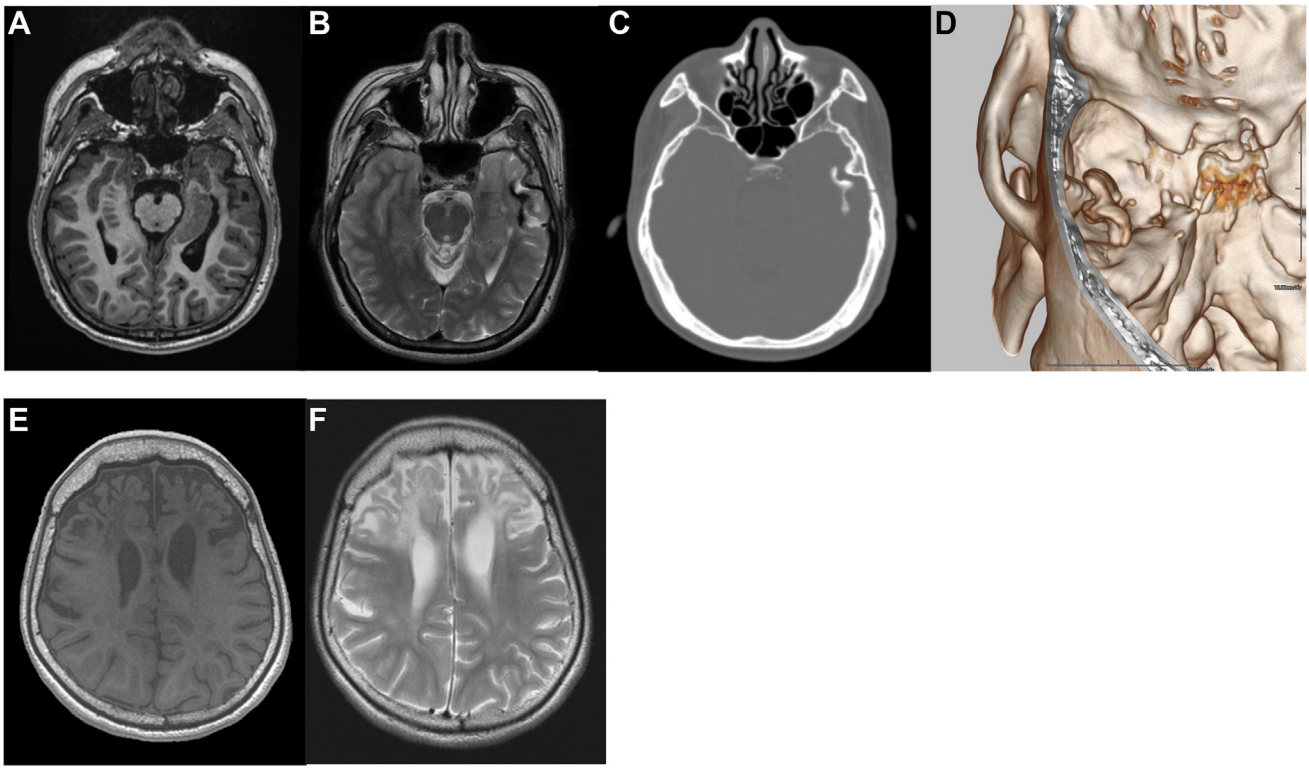

Figure 3. Imaging of the 2 illustrative cases. (**A** and **B**) T1-weighted (A) and T2-weighted (B) magnetic resonance imaging (hippocapal axial plane) in case 1 (patient 1). (**C** and **D**) Computed tomography imaging (**C**) and reconstructed three-dimensional computed tomography image (**D**) in case 1 (patient 1) showing focal skull thickening in the temporal bone. (**E** and **F**) T1-weighted (**E**) and T2-weighted (**F**) magnetic resonance imaging in case 2 (patient 5).

TSC group despite a smaller number of ASMs used compared with the epilepsy group. This suggests that bone thickening in patients with TSC was not due to ASM. Moreover, while females generally have a thicker skull than males,[13] the median thickness of skull was still greater in the TSC group than the NE group despite a lower proportion of female patients in the TSC group, further supporting our findings that patients with TSC have thicker skull.

To the best of our knowledge, 4 types of pathologically thickened skull have been reported to date: nebula frontalis, diffuse calvarial hyperostosis, hyperostosis frontalis interna, and hyperostosis frontoparietalis,[14] all of which involved the frontal cancellous bone except for one that involved the parietal bone. This suggests that the frontal bone is prone to thickening, which is partly in agreement with our findings. This study did not find temporal bone thickening likely because it was conducted during a time when the primary imaging method was radiography, which is a modality that is less optimal for evaluating temporal bone thickness. Occipital bones may be less likely to develop thickening as to our knowledge pathologically thickened occipital bones have not been previously reported.[8]

There were a few case reports on skull thickening[15,16] and a few case series focused on intracranial calcified lesion in patients with TSC.[17,18] However, none have focused on the relationship between skull thickening and intracerebral calcification. We found an association between skull thickening and calcification, suggesting that these 2 manifestations may share a common precipitating factor. Nevertheless, although superficial calcification is more likely to manifest with focal skull thickening, not all superficial calcifications were associated with focal skull thickening, and some were associated with diffuse skull thickening. This suggests that the common precipitating factor possibly occurs both locally and diffusely. A few studies reported the association between bone resorption and TSC1/mTORC1 pathways.[17,19,20] The activation of mTORC1 can cause abnormalities in skeletal development including bone formation and reduction in bone quality.[9,21,22] Although the mechanisms are expected to be more

complex, these signaling pathways may in part play a role as the common precipitating factor of skull thickening and intracerebral calcification in TSC. This pathway may also be responsible for especially the increase in cancellous bone.

Patients with TSC with calcification in the cerebral parenchyma were reported to be more likely to develop pharmacoresistant epilepsy.[23] In general, most epilepsy surgeries involve resection of the frontal and temporal lobes, in which temporal lobe resection accounts for up to 80% of these surgeries.[24] The presence of skull thickening may require some extra attention during craniotomy. For instance, a craniotome with a longer footplate should be prepared during craniotomy involving a diffuse skull thickening. If the planned craniotomy coincides with focal skull thickening such as that in case 1 presented above, slots may be drilled over the thickened spot instead of placing a burr hole or running the footplate through the spot. As patients with TSC with intracerebral calcification are more likely to undergo epilepsy surgery, it is worth considering the possibility of skull thickening during the preoperative planning because the frontal and temporal bones, which are the most common sites for craniotomy for epileptic focus resection, are the most likely to be affected.

This study has several limitations. First, manual measurement of the bone thickness may have introduced some error. Second, we used conventional two-dimensional MRI for measurement instead of three-dimensional MRI because the latter was not available in the majority of patients studied. To account for this drawback, we matched the slice used for measurement as much as possible despite some unavoidable minor measuring point differences among patients. Third, this is a retrospective study in which all clinical data were obtained at the time point of MRI acquisition. Some information, such as previous use of ASMs, may not be reflected in our data. Fourth, we excluded patients <10 years of age. Finally, we were unable to assess genetic factors related to bone thickening because not all the patients underwent genetic testing. We believe that future prospective studies will be necessary to reveal all these factors. Future studies that incorporate genetic testing are warranted to reveal the relationship between intracerebral calcification and skull thickening, or even skeletal abnormalities.

CONCLUSIONS

Patients with TSC have thicker frontal and temporal bones. Skull thickening in patients with TSC is associated with the presence of intracerebral calcification, in which focal thickening is related to subcortical calcifications. This study provides information regarding the skull features that can be useful in determining surgical approaches, such as modifying the technique of craniotomy in the thickened frontal or temporal bone during epilepsy surgery in these patients.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Hideki Kuroda: Writing — original draft, Formal analysis, Data curation, Conceptualization. **Hui Ming Khoo:** Writing — review & editing, Conceptualization. **Yuya Fujita:** Validation. **Koji Tominaga:** Validation. **Kuriko Kagitani-Shimono:** Validation. **Koichi Hosomi:** Validation. **Naoki Tani:** Validation. **Satoru Oshino:** Validation. **Mari Wataya-Kaneda:** Supervision. **Haruhiko Kishima:** Supervision.

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