Temporal encephaloceles in epilepsy patients and asymptomatic cases: Size may indicate epileptogenicity

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Abstract

Objective: This study was undertaken to identify temporal encephaloceles (TEs) and examine their characteristics in patients with temporal lobe epilepsy (TLE) and extratemporal lobe epilepsy (ETLE), as well as in asymptomatic cases.

Methods: Four hundred fifty-eight magnetic resonance imaging scans were examined retrospectively to identify TE in 157 patients with TLE, 150 patients with ETLE, and 151 healthy controls (HCs).

Results: At least one TE was identified in 9.6% of the TLE patients (n = 15, 95% confidence interval [CI] = 5.3%–15.3%), in 3.3% of patients with ETLE (n = 5, 95% CI = 1.1%–7.6%), and in 2.0% of the HCs (n = 3, 95% CI = .4%–5.7%), indicating a significantly higher frequency in patients with TLE compared to ETLE and HC subjects (p = .027, p = .005). Examining the characteristics of TEs in both asymptomatic and epilepsy patients, we found that TEs with a diameter of less than 6.25 mm were more likely to be asymptomatic, with a sensitivity of 91.7% and a specificity of 73.3% (area under the curve = .867, 95% CI = .723–1.00, p = .001).

Significance: Temporal encephaloceles may occur without presenting any clinical symptoms. Patients with TLE show a higher frequency of TEs compared to the ETLE and HC groups. According to our study, TE size could be used to suggest potential epileptogenicity.

Keywords

asymptomatic temporal encephaloceles, epilepsy surgery, MRI-negative epilepsy, temporal encephaloceles, temporal lobe epilepsy

Key Points

- Small TEs were identified in three of 151 healthy subjects (2.0%)
- The frequency of TEs in the TLE group was significantly higher compared to the ETLE group and the HC group
- TEs with a diameter of less than 6.25 mm were significantly more likely to be asymptomatic
1 | INTRODUCTION

Encephaloceles are protrusions of brain parenchyma through the middle fossa and skull base. Temporal encephaloceles (TEs) can be congenital, associated with intracranial hypertension, increased body mass index (BMI), chronic inflammation, neoplasia, trauma, or iatrogenic conditions. They may be asymptomatic, but they are usually diagnosed due to cerebrospinal fluid (CSF) leaks, hearing loss, recurrent meningitis, and temporal lobe epilepsy (TLE). TEs can be congenital, associated with intracranial hypertension, and temporal lobe epilepsy (TLE). They may cause epilepsy, either by mechanical irritation of brain parenchyma or due to their secondary association with other structural lesions, such as gliosis, cortical dysplasia, and neuronal heterotopia. Recent literature suggests that the prevalence of TEs in patients with refractory TLE varies between 1.9%, 4%, and 12.5%. Although their role in the presurgical evaluation still remains controversial, many case series show a positive outcome after surgical treatment of patients with refractory TLE and TEs. Their identification is particularly important in cases previously considered to be magnetic resonance imaging (MRI)-negative, influencing surgical planning, and consequently, the clinical outcome in patients with refractory TLE.

Because TEs are mostly identified in symptomatic patients, their prevalence and their characteristics have not yet been reported among healthy populations. A few studies have examined the frequencies of TEs in healthy controls (HCs) or patients with other neurological conditions, but with inconclusive results. Reviewing and comparing the characteristics of TEs between asymptomatic patients and patients with epilepsy may provide useful information concerning their clinical role. Therefore, we aimed to examine the significance and imaging characteristics of TEs, not only in patients with TLE, but also in patients with extratemporal lobe epilepsy (ETLE), as well as in HCs.

2 | MATERIALS AND METHODS

2.1 | Study design and clinical data

We retrospectively reviewed 458 MRI scans in three different study populations. The first group consisted of 157 patients with TLE, the second group of 150 patients with ETLE, and the third group of 151 HCs. Patients with structural epilepsy were not excluded from the TLE and ETLE groups. All epilepsy patients were treated at the Epilepsy Center Hessen in Marburg, Germany between 2008 and 2018. The localization of the epileptogenic zone was determined by experienced epileptologists from our center during an in-house evaluation, which included video-electroencephalographic (EEG) monitoring, MRI, and presurgical assessment. Clinical management and the recommendation for epilepsy surgery were not influenced by the results of this study, as our data were collected retrospectively. The postsurgical outcome was reviewed based on available follow-up data. MRI scans of the HC group were obtained from our anonymized HC database, which was established for research purposes between 2010 and 2011. The clinical information provided in the HC group included age, sex, and absence of any neurological condition. The study was approved by the local ethics committee. We followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to minimize methodological biases.

2.2 | Imaging

All patients underwent either 1.5- or 3-T MRI imaging between 2008 and 2018 at our center or at external MRI scanners. Because all MRI scans were conducted for clinical purposes, the protocols used were not identical. However, all patients had an axial and a coronal spin-echo T1 scan or a three-dimensional T1-weighted scan, a coronal cube fluid-attenuated inversion recovery, and an axial diffusion sequence. The HC MRI scans were conducted between 2010 and 2011, including magnetization-prepared rapid acquisition with gradient echo sequences on a 3-T MRI scanner (Trio Siemens).

2.3 | Statistical analysis

Continuous variables are presented as median (range) and categorical variables as proportions. Quantitative variables were compared using Student t-test and Mann–Whitney U test and qualitative variables (e.g., gender) using chi-squared test or Fisher exact test, as appropriate. Wilson 95% confidence intervals (CIs) were computed for the frequencies of TEs in the three study populations. All reported probability values (p-values) are based on two-sided tests; the level of statistical significance was set at $\alpha = .05$. Receiver operating characteristic (ROC) curve analysis was used to identify the optimal cutoff value according to the Youden index. Analyses were performed using SPSS 23.0 (IBM, 2017).

2.4 | Definitions and measures

TEs were defined as asymptomatic if they occurred in the HC and ETLE patient groups, or contralateral to the assumed epileptogenic zone in the TLE patient group, whereas they were defined as “probably epileptogenic” if they occurred ipsilateral to the assumed epileptogenic zone of TLE patients, without another coexisting structural lesion considered as most likely epileptogenic. Unilateral TEs in patients with...
<table>
<thead>
<tr>
<th>Case</th>
<th>Age/epilepsy onset, years/sex</th>
<th>Epilepsy focus</th>
<th>TEs, n</th>
<th>Localization</th>
<th>Diameter, mm</th>
<th>Initial MRI findings</th>
<th>TE supposed to be epileptogenic</th>
<th>Epilepsy surgery</th>
<th>TE removed</th>
<th>Outcome</th>
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<tr>
<td>1</td>
<td>26/15/m</td>
<td>TLE R</td>
<td>2</td>
<td>1. AT R</td>
<td>R: 7.8</td>
<td>No lesion</td>
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<td>N/A</td>
<td>Follow-up data</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>2. AIT L</td>
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<td></td>
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<tr>
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<td>AT L</td>
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<td>Probably</td>
<td>No</td>
<td>N/A</td>
<td>Follow-up data</td>
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<td>HS</td>
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<td>11</td>
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<td>No</td>
<td>No</td>
<td>1 Sz/month under medication</td>
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<td>2</td>
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<td>Glioma temporal lobe</td>
<td>No</td>
<td>Yes/glioma surgery</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>2. AIT L</td>
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<td></td>
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<td>TLE L DD PLE</td>
<td>1</td>
<td>AIT L</td>
<td>8.4</td>
<td>Low-grade glioma parietal lobe</td>
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<td>ALTR</td>
<td>6.2</td>
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<td>AIT L</td>
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<td>No</td>
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<td>AT R and L</td>
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<td>R: No</td>
<td>No</td>
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<td>L: 7.4</td>
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<td>No</td>
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<td>AT L</td>
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<td>4–5 Sz/month</td>
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<td>No</td>
<td>1 Sz/month under medication</td>
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<td>2</td>
<td>ALTR and L</td>
<td>1. R: 6.5</td>
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<td>No</td>
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<td>2. L: 5.7</td>
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<td>18</td>
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<td>AIT R</td>
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<td>Double cortex</td>
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(Continues)
bitemporal TLE were considered epileptogenic. In the present study, the size of TEs was reported according to their maximal diameter.2,7

2.5 | Data availability statement

Anonymized data will be shared upon request with any qualified investigator.

3 | RESULTS

3.1 | Study groups and demographic and clinical characteristics

The TLE patient group consisted of 157 patients (49.7% female, n = 78) with a median age of 42 years (range = 17–78 years), the ETLE patient group consisted of 150 patients (43.3% female, n = 65) with a median age of 34 years (range = 7–70 years), and the HC group consisted of 151 subjects (45% female, n = 68) with a median age of 33 years (range = 28–47 years). Distribution of age did not differ significantly between the TLE group and the ETLE (p = .661) and HC (p = .627) groups. Similarly, sex distribution did not differ significantly among the TLE group and the ETLE (p = .265) and HC (p = .414) groups. The initial MRI findings of epilepsy patients in the first two groups were as follows: in 52.8% (n = 162), no lesion was found; in 9.1% (n = 28), hippocampal sclerosis was identified; and in 38.1% (n = 117), other lesions were diagnosed.

3.2 | Imaging and clinical findings

At least one TE was identified in 23 of the 458 MRI scans (5.0%). The total number of identified TEs was 27. TEs were unilateral (82.6%) in 19 patients and bilateral in four patients (17.4%). In the TLE patient group, at least one TE was identified in 15 of 157 scans (9.6%, 95% CI = 5.3%–15.3%). There were 12 patients with unilateral TEs and three with bilateral TEs in this group. All patients with bilateral TEs had a unilateral epileptogenic zone (Table 1, Cases 1, 8, and 13). One of these three patients (Table 1, Case 8) had a glioma that was ipsilateral to the epileptogenic zone, which was considered to be the epileptogenic lesion in this case. Two patients with unilateral TEs had a bitemporal epileptogenic zone (Table 1, Cases 14 and 15), and one patient had an epileptogenic zone that was contralateral to the TE (Table 1, Case 3; Figure 1). Overall, TEs in 12 of 15 patients in this group (80%) could be considered to be “probably epileptogenic” because they were identified as being ipsilateral to the epileptogenic zone, without any other most probable epileptogenic lesion.
Moreover, TEs were identified in five of 150 MRI scans (one bilateral and four unilateral) in the ETLE patient group (3.3%, 95% CI = 1.1%–7.6%) and in three of 151 MRI scans in the HC group (2.0%, 95% CI = .4%–5.7%). On the initial examination of the same MRI scans, a TE was identified in only one patient of the 23. The abovementioned results are presented in Table 1. Representative images are presented in Figure 2.

A significantly higher frequency of TEs was found in the TLE group compared to the ETLE group ($p = .027$) and the HC group ($p = .005$), whereas no significant difference was seen between the ETLE and HC groups ($p = .468$).

We aimed to examine the characteristics of asymptomatic TEs and those considered epileptogenic after evaluating clinical, MRI, and EEG data. Asymptomatic and symptomatic TEs differed significantly in size when comparing the diameter (median 5.8 vs. 8.15 mm, respectively, $p = .01$). Using ROC curve analysis (Figure 3), we found that TEs with a diameter of less than 6.25 mm were more likely to be asymptomatic, with a sensitivity of 91.7% and a specificity of 73.3% (area under the curve $= .867$, 95% CI = .723–1.00, $p = .001$).

Overall, four of 12 TLE patients were considered to have epileptogenic TEs and underwent epilepsy surgery because of refractory TLE. TEs were removed in two of four surgically treated patients, with the epileptogenic zone ipsilateral to the TE. After a median follow-up of 60 months (range = 24–84 months), these two patients remained seizure-free (Engel Class IA), one after a standard temporal lobectomy (Table 1, Case 4) and the other after a lesionectomy (Table 1, Case 6). The patient treated with lesionectomy was the only one initially diagnosed with a TE. The other two patients underwent epilepsy surgery due to another potentially epileptogenic lesion, without resection of the TE. One patient had an amygdalohippocampectomy of a hippocampal sclerosis (Table 1, Case 5), and one patient had a lesionectomy of a parietal lesion (Table 1, Case 9). Both patients were not seizure-free following surgery (Engel Class IIIA). A total of six of 12 patients refused further invasive presurgical evaluation or surgical treatment. In the remaining two patients, no further diagnostic assessment was recommended because of satisfactory seizure control under medication.

4 | DISCUSSION

TEs can easily be missed due to a lack of symptoms, their small size, and MRI limitations in identifying bone deficits, as well as limited awareness.2,3,7,8,17,19 Systematic MRI review and reporting raise the sensitivity of TE detection.17,22 The sequences most helpful in identifying TEs are T2-weighted sequences, as they provide a better contrast between CSF, bone, and brain parenchyma tissue.17 Ideally a balanced steady-state gradient echo sequence with its high signal-to-noise ratio and its enhanced spatial resolution of thin MRI slices might be helpful to depict smaller TEs.23 However, in our study MRIs were acquired in a routine clinical setting. Most TEs in this study were identified in T1 sequences, as this sequence was available in all protocols. Additional computed tomographic scans can be helpful to confirm bone abnormalities.8,17

The frequencies of TEs reported in this study are in line with those of previous studies regarding the TLE patient group (9.6%) and are slightly higher in the ETLE patient group (3.3%).8 In contrast to previous studies that included control groups,8,16 we could identify small TEs in three of 151 healthy subjects (2.0%). The frequency of TEs in the TLE group was significantly higher compared to the ETLE group and the HC group, supporting the well-established association of TEs with TLE either as possible epileptogenic lesions or indicators of epileptic tissue.2,7,8,11,13,18,20 There was no significant difference when comparing the frequency of TEs between the ETLE and HC groups, suggesting that TEs may be an incidental finding in ETLE patients too.

The occurrence of nonepileptogenic TEs in TLE patients has been reported, mainly in patients with bilateral TEs who remained seizure-free after unilateral surgery.4,7,8,11,12 In this study, there were three patients identified with bilateral TEs.
and a unilateral temporal epileptogenic zone; one patient with an epileptogenic zone contralateral to the identified TE (Figure 1), as well as two patients with unilateral TEs and bitemporal epileptogenic zones. Furthermore, identifying asymptomatic TEs in the HC group raises the question of when TEs should be considered a nonspecific finding and which characteristics can be indicative to classify them as probably epileptogenic or not. We found a significant correlation between the size of TEs and the probability that they were considered epileptogenic. TEs with a diameter of less than 6.25 mm were more likely to be asymptomatic. This association could be explained by the mechanical irritation of brain parenchyma, as a mechanism suggested previously, primarily associated with larger rather than smaller TEs. Another hypothesis may be that larger TEs could be more frequently associated with other brain parenchyma abnormalities, showing brain developmental anomalies. These results should be used with caution, providing additional information to clinical and EEG data.

Identification of TEs is essential in the presurgical evaluation of TLE patients, especially in cases considered to be MRI-negative, as epilepsy patients with identified MRI lesions have better surgical outcome than MRI-negative patients. As literature reviews suggest, most patients with TEs and refractory TLE who underwent surgery remained seizure-free. In our study, both surgically treated patients who underwent resection of TE remained seizure-free (Engel Class IA), whereas surgically treated patients with dual pathologies without resection of the TE continued to have seizures after surgery (Engel Class IIIA).

The suitable surgical treatment of patients with refractory TLE and TEs has been intensively discussed and depends mainly on the classification of the TE, either as epileptogenic itself or as a marker of epileptic tissue, as well as on the presence of other pathologies, such as hippocampal sclerosis. The surgical options mainly discussed are lesionectomy, including or excluding mesiotemporal structures, such as amygdala and hippocampus, and standard temporal lobectomy. In the present study, one patient remained seizure-free 60 months...
after lesionectomy (Engel IA), suggesting that this procedure is a feasible option, as already shown in other reported cases.\(^3\)\(^1\)\(^1\) On the other hand, the association of TEs with other MRI-negative epileptogenic lesions should be considered when selecting more extensive surgical procedures, such as standard temporal lobectomy. Intracranial stereo-EEG (SEEG) and MRI findings have shown frequent involvement of mesial temporal structures in patients with TEs.\(^8\)\(^1\)\(^1\)\(^7\)\(^2\)\(^5\) A recent literature review by de Souza et al.\(^2\)\(^5\) suggests that lesionectomy combined with amygdalohippocampectomy may provide a better surgical outcome regarding seizure freedom than lesionectomy alone, but with worse neuropsychological outcome. The authors suggested using SEEG methods to reduce unnecessary hippocampal resection, especially in cases with no hard evidence of hippocampal pathology.\(^2\)\(^5\) Overall, the available data concerning the best surgical treatment in patients with TEs are limited; therefore, the surgical decision should be individualized.

The present study has certain limitations, especially because of its retrospective character. STROBE guidelines were followed to minimize methodological biases.\(^2\)\(^1\) As already mentioned above, the available MRI data were not standardized for all subjects examined and were conducted for clinical purposes, possibly leading to a higher number of false negative MRI findings. Additionally, BMI was not available for all patients and controls, and therefore its association with the occurrence of TEs could not be examined. Moreover, the limited number of TEs identified should be considered when interpreting the statistical results.

5 Conclusions

The detection of TEs influences the clinical and surgical decision during the presurgical evaluation of TLE patients. TEs should be considered as possible epileptogenic lesions or indicators of epileptic tissue in patients with TLE, if their localization is concordant with other indicators of the epileptogenic zone. The recommended surgical treatment should be individualized in refractory cases. TEs with a diameter of less than 6.25 mm were more likely to be asymptomatic. In such patients, further investigation of other epileptogenic lesions should be considered, using more advanced methods such as invasive EEG evaluation.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Panagiota-Eleni Tsalouchidou: study concept and design, writing of manuscript, data analysis and interpretation, revision of manuscript. Ioannis Mintziras and Louise Biermann: interpretation of data, statistical analysis, revision of manuscript. Kristina Krause: major role in acquisition of data, study concept and design, revision of manuscript. Marc-Philipp Bergmann, Marcus Belke, and Christopher Nimsky: major role in acquisition of data. Maximilian Schulze: major role in acquisition of data, and data analysis and interpretation. Adam Strzelczyk and Felix Rosenow: major role in acquisition of data, study design, and revision of manuscript. Katja Menzler and Susanne Knake: study concept and design, data analysis and interpretation, revision of manuscript.

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