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Characteristics of bilateral versus unilateral temporal encephalocele-associated epilepsy

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ABSTRACT

Purpose: To characterise bilateral temporal encephalocele (BTE)-associated epilepsy relative to unilateral temporal encephalocele (UTE)-associated epilepsy as a rare but curable cause of structural epilepsy using demographics, epilepsy status and imaging findings.
Method: In this single-centre retrospective study we included all patients from June 2015 to August 2018, who suffered from epilepsy and were diagnosed with a temporal encephalocele. Data were systematically collected and analysed for differences between BTE and UTE.
Results: Seventeen epilepsy patients diagnosed with temporal encephaloceles (TE) were identified. One-third exhibited BTE. The age of epilepsy onset was higher in patients with BTE compared to UTE (median 51 vs. 37 years, $p = 0.074$). Latency between epilepsy diagnosis and definitive TE diagnosis differed considerably with a median five-fold shorter duration for the BTE-group when compared to the UTE-group (2–10 years, $p = 0.02$). Five of seven (81%) patients with BTE were pharmacoresistant, while this applied to only five out of ten (50%) patients with a UTE.
Conclusion: When compared to UTE-associated epilepsy, BTE-associated epilepsy is characterised by a later age at onset, shorter delay in TE diagnosis and more frequent drug-resistance. As epilepsy surgery is a valid treatment option for both syndromes, a standardised diagnostic workup should be implemented for temporal lobe epilepsy (TLE) patients with unknown aetiology to facilitate early detection of UTE and BTE.

1. Introduction

Temporal lobe encephaloceles (TEs) are defined as a pathological herniation of brain parenchyma through a dural and/or bony defect in the middle cranial fossa [1,2]. Their aetiology remains controversial. Most TEs seem to be congenital, although symptomatic forms have been reported, and are typically associated with local inflammation, trauma, neoplasia or idiopathic intracranial hypertension [3–5].

TEs are asymptomatic in the majority of cases. Infrequently, however, they are associated with CSF leakage, which can manifest as otorrhoea or rhinorrhoea, and may even lead to recurrent meningitis with direct neurological complications such as weakness or sensory disturbances [6–9]. TE has been found in up to 1.9% of patients with drug-refractory TLE and in 10% of patients operated on for TLE [10]. Mechanical irritation or secondary gliosis of the adjacent cortex has been considered a possible cause [2,11–13].

The increasing frequency of TEs reported over recent decades is most likely explained by enhanced quality of MRI and other imaging techniques and growing awareness rather than a true increase in prevalence [10,14,15]. Epilepsy surgery, including lesionectomy, temporal pole resection or lobectomy, used to gain seizure freedom or a reduction in seizure frequency has been reported in the majority of cases. Thus, highlighting the relevance of a TE diagnosis in TLE patients [5,10,11,14,16,17].

The majority of patients with TE-associated epilepsy show only unilateral effects on the middle cranial fossa, but bilateral TEs can occur [5,10,16,17]. However, no report has focussed on patients suffering

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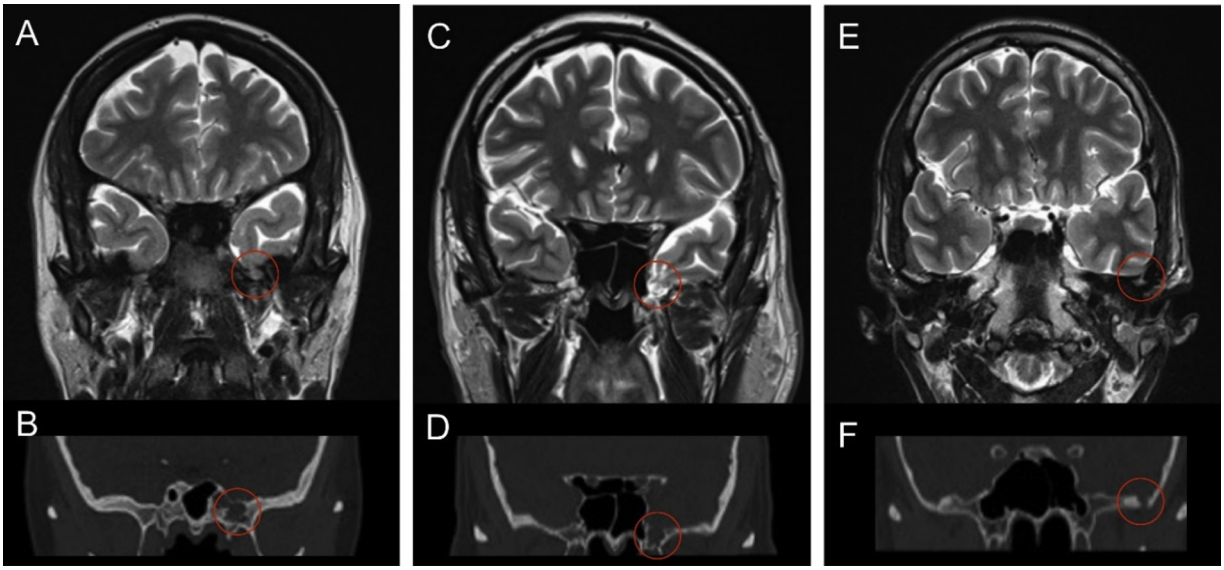

Fig. 1. Representative images of three patients with unilateral lesions. Images A/C/E show coronal T2-weighted sequence of 3 T MRI; Images B/D/F show CT of the associated bony defect of the skull base. Lesions are circumscribed by a red circle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

from BTE-associated epilepsy. Characterizing BTE-associated epilepsy may provide important information regarding the aetiology and management of TEs in this setting. Here, we report a single centre case series focussing on defining BTE-associated epilepsy in comparison to UTE-associated epilepsy and the specific challenges associated with this syndrome.

2. Patients and methods

2.1. Study design

All out- and inpatients suffering from focal epilepsy with at least one temporal lobe encephalocele, detected from June 2015 to June 2018 at the Epilepsy Centre Frankfurt Rhine Main, were included in this retrospective study. Demographic features, epilepsy-related data and imaging findings were systematically ascertained. This analysis is part of a study on epilepsy outcomes that was approved by the local ethics committee. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and RECORD (Reporting of Studies Conducted using Observational routinely-collected Data) guidelines were followed [18–20].

2.2. Epilepsy-related data

The diagnosis was based on reported or videographically documented seizure semiology and the interictal and (if present) ictal EEG-findings, which were evaluated by at least two experienced epileptologists [21]. The classification of seizure types, epilepsies and drug resistance was based on the definitions proposed by the ILAE and the semiological seizure classification by Luders et al. [22–26]. Additionally, auras and seizures were analyzed for localizing signs or symptoms as descriped in the review of Loddenkemper et al [27]. Referring to this, automotoric seizures (with manual or oral automatisms) and epigastric/mental auras were assigned to have a temporal origin. Based on the findings, epilepsy was classified as temporal lobe epilepsy (TLE) or extratemporal lobe epilepsy (ETLE). If a severe traumatic brain injury happened not more than 12 months before the epilepsy started, the etiology of the TE was suggested to be traumatic. If there was a history of meningitis not more than 12 months before the onset of epilepsy, the etiology was suggested to be “inflammatory”. If there was no hint for a traumatic or inflammatory genesis, the etiology was labelled as “spontaneous”. The definition of cortical zones were based on the established concept by Lueders et al. [28]. Epilepsy-related data were registered. Seizure freedom was defined as a seizure-free period of longer than 12 months.

2.3. Imaging technique and analysis

All patients underwent a specific epilepsy protocol in a 3 T MRI-Scanner (Verio or Skyra fit, Siemens, Erlangen, Germany). The protocol included a three-dimensional T1-weighted volume data set with 1 mm slice thickness (MPRAGE), a T2 fluid-attenuated inversion recovery (FLAIR)-weighted 3D dataset with 1 mm slice thickness (both 3D sequences reconstructed in axial and coronal orientation and surface-rendered (Mercator projection)) and T2-weighted TSE-sequences in axial (5 mm) and coronal (3 mm) orientation, diffusion-weighted images with apparent diffusion coefficient (ADC)-maps as well as T2*-weighted or susceptibility-weighted (SWI) sequences. In 15 of 17 patients, an additional CT-scan of the skull base was available. Imaging data were evaluated by an experienced senior neuroradiologist (MW). TE was diagnosed when temporal brain parenchyma surrounded by CSF bulged out into a cranial bony defect (Fig. 1). The volume of the temporal herniation was calculated by measuring the three-dimensional extent of the encephaloceles using the 1 mm slice T2-weighted images and applying the ABC/2 formula [29]. In patients with more than one TE, all encephaloceles were measured separately. MRI-scans were analyzed for additional findings, especially potentially epileptogenic lesions (e. g. hippocampal sclerosis) as well as for conceivable risk factors for the development of TE (e. g. hydrozephalus, benign intracranial hypertension). If other pathological findings were identified, they were documented descriptively.

2.4. Data management and analysis

Data were recorded in EXCEL 2016 (Microsoft Inc., Redmond, USA) and analysed using IBM SPSS Statistics 22 (IBM Software Inc., Armonk, USA). Figures were designed using Pixelmator (Pixelmator Team Ltd. & Apple Inc., Cupertino, USA). Data were analysed for all patients together and separately for patients with UTE and BTE. Frequency and percentages were calculated for categorical variables. Descriptive analysis, including median and range, as well as a bivariate *Mann Whitney U* test was performed for quantitative variables. P-values < 0.05 were

Table 1
Patient´s demographic characteristics, epilepsy related information and MR-findings.

Patient	Age (years)/ sex	BMI (kg/m^2)	Onset epilepsy in years/latency to diagnosis TE in years	Aura/Seizure types	epilepsy syndrome	Number of TE, Localization TE, side /Volume (mL)	Other imaging findings	video-EEG-findings	Seizure frequency	History of medication (current medication in bold print)	Surgical inter-vention/ outcome	Suggested etiology
Patients with unilateral TE												
1	48/m	29.9	40/7	gustatoric aura/ sGTCS	TLE	1. left tb / 0.24	left amygdalar enlagement	IZ and SOZ: left temporal	> 1 /month	**BRV**, LEV, **LTG**, OXC, PHT, VPA	no	unknown
2	61/m	27.4	53/5	-/automotoric seizure	TLE	1. right tl / 0.12	none	–	SF	**LCM**	no	unknown
3	35/m	22.0	31/3	-/sGTCS	unknown	1. left tb / 0.01	none	–	SF	**LEV**	no	unknown
4	28/m	22.0	13/13	-/hypermotoric seizure, sGTCS	ETLE	1. left tm / 0.07	none	SZ: frontal, no EEG patterns	> 1/week	CBZ, LEV, **LTG, OXC**	no	unknown
5	41/f	24.6	39/5	-/automotoric seizure	TLE	1. left tb / 0.05	DVA frontal right	IZ: left temporal	unknown	**LTG**	no	traumatic (traumatic brain injury)
6	31/m	26.0	7/24	-/sGTCS	ETLE	1. left tb / 0.25	none	IZ and SOZ: left frontocentral	> 1/month	ESC, LCM, LEV, **LTG**, OXC, **PER**, ZNS	no	traumatic (traumatic brain injury)
7	51/m	34.4	49/0	-/SGTC	ETLE	1. right tb / 0.06	none	IZ: bioccipital	SF	**LEV**	no	unknown
8	62/m	46.3	35/25	epigastric aura/ automotoric seizure, sGTCS	TLE	1. right tb / 0.04	DVA temporal right	IZ: right temporal	SF	**BRV**, CBZ, LEV, **LTG**	no	unknown
9	50/f	29.4	36/15	unspecific aura/ automotoric seizure, sGTCS	TLE	1. right tb / < 0.01	none	IZ and SOZ: right temporal	> 1/week	**LCM**, LEV, LTG, OXC, TPM, VPA, **ZNS**	no	unknown
10	64/m	unknown	37/27	unspecific aura/ automotoric seizure	TLE	1. left tp / 0.09 2. left tl / 0.16	left hippocampal sclerosis	–	SF	**LEV, LTG**	no	unknown
Patients with bilateral TE												
11	71/f	25.7	67/0	epigastric aura/ automotoric seizure	TLE	1. right tm / 0.77 2. right tp / 0.27 3. left tb / 0.15	left amygdalar enlargement	IZ: right temporal	SF	LCM, LEV, LTG, ZNS	no	unknown
12	23/m	21.3	10/10	mental aura/ automotoric seizure, sGTCS	TLE	1. right tp / 0.20 2. left tp / 0.02 3. left tp / 0.06	none	IZ: right temporal	SF	LEV, LTG, STM, VPA	Temporal lobe resection r including the hippocampus/ Engel 1 a/ILAE 1	unknown
13	68/m	25.0	66/1	-/automotoric seizure, dialeptic seizure	TLE	1. right tp /0.22 2. left tp / 0.22	hydrocaphalus	–	> 1/month	LCM, LEV, TPM,VPA	no	unknown
14	50/f	49.8	50/1	mental aura/ automotoric seizure, sGTCS	TLE	1. right tb /5.04 2. left tb / 0.39	none	IZ and SOZ: left > right temporal	SF	BRV, CBZ, LCM, LEV, LTG, OXC	Temporal pol resection l excluding the hippocampus/ Engel 1 a/ILAE 1	unknown
15	81/m	23.7	76/4	-/automotoric seizure, dialeptic seizure	TLE	1. left tp / 0.04 2. right tp / 0.07	hydrocaphalus	–	> 1/week	LEV	no	unknown
16	39/f	30.5	37/3	epigastric aura/ automotoric seizure, sGTCS	TLE	1. left tb / 0.11 2. right tb / 0.03	benign intracranial hypertension	IZ and SOZ: right temporal	> 1/week	LEV, LTG	no	spontaneous

(*continued on next page*)

Table 1 (*continued*)

Patient	Age (years)/ sex	BMI (kg/m^2)	Onset epilepsy in years/latency to diagnosis TE in years	Aura/Seizure types	epilepsy syndrome	Number of TE, Localization TE, side /Volume (mL)	Other imaging findings	video-EEG-findings	Seizure frequency	History of medication (current medication in bold print)	Surgical inter-vention/ outcome	Suggested etiology
17	55/m	unknown	51/2	-/sGTCS	unknown	1. left tb / 0.17 2. right tb / 0.07	none	–	SF	LEV	no	inflammation (recurrent middle ear infections, meningitis)

Abbreviation: yyear; f = female; m = male, BMIbody-mass-index; TEtemporal encephalocele; SGTCsecondary generalized tonic-clonic seizure; TLEtemporal lobe epilepsy; ETLExtratemporal lobe epilepsy, SF.seizure free; BRVbrivaracetam, CBZ: carbamazepine, LCM: lacosamide, LTG: lamotrigine, LEV: levetiracetam, OXC: oxcarbazepine, PHT: phenytoin, STM: sulthiame, TPM: topiramate, VPA: valproate, ZNS: zonisamide, No: Number, tb: temporobasal, tp: temporopolar, tm: temporomesial, tl: temporolateral, t: temporal; IZirritative zone; SOZseizure onset zone; rright, l:left; DVAdevelopmental venous anomaly.

considered significant.

3. Results

3.1. Study population and demographic results

A total of 17 patients (seven women) were retrospectively identified and diagnosed with TE-associated epilepsy, of which seven (three women) showed BTE-associated epilepsy. The median age was 50 years [range 23–81] for the entire study population, 49 years [range 28–62 years] within the UTE cohort and 55 years [range 23–81 years] within the BTE cohort. The body mass index (BMI) of the patients did not differ significantly within the cohorts and ranged between 27.4 kg/mm^2 [range 22.0–36.3] within the unilateral cohort and 25.3 kg/mm^2 [range 21.3–49.8] within the bilateral group (Table 2).

3.2. Epilepsy-related data

All patients included in this study suffered from focal epilepsy, which had been labelled as 'lesion-negative' prior to consulting our institution. The median age at epilepsy onset differed widely between the bilateral and unilateral groups. We detected that patients with BTE-associated epilepsy were considerably older at onset than patients with UTE-associated epilepsy (median age 51 y vs. 37 years, p = 0.074). In addition, BTE patients had TLE more frequently (86%) than UTE patients (70%). Supporting this data, a total of four out of seven patients with BTE reported an aura localizing to the mesiotemporal region (epigastric or mental), while only four out of 10 patients with UTE reported epigastric, gustatoric or non-specific auras.

The latency from epilepsy to TE diagnosis was a median of 2 years in the BTE group, which was significantly shorter than in UTE patients with UTE with a median of 10 years (p = 0.02) (Table 2). In both groups, different seizure types including automotoric, dialeptic seizures (both focal unaware seizures) and secondary generalised tonic-clonic seizures, were detected. Interestingly, there were no significant differences in the suggested aetiology of the encephaloceles between the bilateral and unilateral groups. Five of seven patients from the bilateral cohort were drug resistant. In comparison, only five out of ten patients with UTE were drug resistant. Two of five patients with BTE-associated epilepsy underwent surgical intervention, while all patients with a UTE received only anticonvulsant treatment. One male BTE patient (patient #12 Table 1 , Fig. 2A, B and C), who underwent surgical treatment, presented with an irritative zone and a seizure onset zone exclusively on the right side and subsequently underwent right temporal lobectomy including the hippocampus. At the two-year follow-up he was seizure free (Engel 1a, ILAE 1). Histopathology showed gliosis around the TE. A female patient (#14 of Table 1, Fig. 2G, H, J and I) who underwent left temporal lobe resection sparing the hippocampus, showed bilateral but predominantly left-sided irritative and seizure onset zones. The histopathological workup of removed brain tissue showed no signs of focal cortical dysplasia, dysmorphia or tumour. At the one-year follow-up, she remained seizure free (Engel 1a, ILAE 1). For details, please refer to Table 1.

3.3. Imaging features

The median volume of the TE was 0.09 ml for the entire study population. We found a tendency toward greater encephaloceles volume in patients with BTE compared to UTE (0.12 to 0.07 ml, without statistical significance (p = 0.23). In both groups, additional imaging pathologies were identified in approximately 50% of the study population (see Table 1 for details).

4. Discussion

TEs represent a potentially curable cause of epilepsy and seem to be

Table 2
Clinical characteristics (demographic findings, epilepsy related data and imaging findings).

		Total (n = 17)	Unilateral TE (n = 10)	Bilateral TE (n = 7)	Significance (α = 0,05)
Demographic findings					
Age (y)*		50 [23-81]	49 [28-62]	55 [23-81]	*p = 0.33*
Sex (m/f)**		12/5	8/2	4/3	
BMI (kg/m^2)*		26 [21.3-49.8] (n = 15)	27.4 [22.0-36.3] (n = 9)	25.3 [21.3-49.8] (n = 6)	p = 0.75
Epilepsy related data					
Epilepsy onset(y)*		39 [7-76]	37 [7-53]	51 [10-76]	p = 0.074
Epilepsy syndrome (TLE // ETLE // unclear) **		12/17 (71%) // 3/17 (17%) // 2/17 (12%)	6/10 (60%) // 3/10 (30%) // 1/10 (10%)	6/7 (86%) // 0 // 1/7 (14%)	
Latency to diagnosis of TE (y)*		5 [0-25]	10 [0-25]	2 [0-10]	p = 0.02
Seizure type **	AS	11/17 (65%)	5/10 (50%)	6/7 (86%)	
	DS	2/17 (12%)	1/10 (10%)	2/7 (29%)	
	SGTC	11/17 (65%)	7/10 (70%)	4/7 (57%)	
Suggested etiology **	spontaneous	14/17 (71%)	8/10 (80%)	6/7 (86%)	
	inflam	1/17 (6%)	0/10 (0%)	1/7 (15 %)	
	traumatic	2/17 (17%)	2/10 (20%)	0	
No. of medication *		3,4 [1–7]	3,4 [1–7]	3,4 [1–6]	
Refractory to medication **		10/17 (59%)	5/10 (50%)	5/7 (71%)	
Surgical intervention **		2/17 (12%)	0	2/7 (29%)	
MR-findings					
Volume in mL*		0,09 [0,0-5,04]	0,07 [0,0-0,64]	0,12 [0,02-5,04]	p = 0.23
Other imaging findings **		8/16 (53%)	5/10 (50%)	4/7 (57%)	

Abbreviation and explanation: *median [range]; ** frequency (percentage); abbreviations: y: year; f = female; m = male, BMI: body-mass-index;TLE: temporal lobe epilepsy; ETLE: extratemporal lobe epilepsy; TE: temporal encephalocele; AS: automotoric seizure; DS: dialepetic seizure; SGTC: secondary generalized tonic-clonic seizure; inflam: inflammatory; No: Number.

an ideal target for personalised therapeutic approaches. In contrast to previous case series, we specifically aimed to characterise BTE- in comparison to UTE-associated epilepsy. This information is important for diagnostic strategies and therapeutic aspects such as surgical resection. Consistent with previous studies [5,10,16,17], we showed that seizure freedom can be achieved by temporal lobe resection, even in patients with BTE. Our study confirms the results of previous studies and shows a relevant delay in TE diagnosis with a median latency of about five years. Interestingly, bilateral presentation was a positive predictor for earlier detection (median latency of 2 years, p = 0.02) [5,10,16,17]. This finding supports the importance of being aware of TE-associated epilepsy, especially in patients labelled as 'lesion-negative', as previously proposed by Campbell and colleges [15]. Furthermore, there is need for a standardised workup in these 'lesion-negative' patients, which should consist of a standardised imaging programme and systematic interdisciplinary review with special attention to the inferior temporal lobe borders [21]. The value of CT reconstruction of the middle cranial fossa as a standard procedure remains to be investigated. Analyzing the types of seizures and auras, we did not find a clinical sign or symptom, which is specific for the entity of TE, however they seem to be associated with types of auras and seizures localizing to the mesiotemporal region (e. g. epigastric or mental auras, automotoric seizures).

The most interesting and still controversial aspects of TE are the aetiology and pathogenesis. In a recent case series, Urbach et al. postulated an association between encephaloceles and benign hypertension and obesity [5]. The results of our study support this hypothesis to some extent; one patient was diagnosed with benign intracranial hypertension, and two subjects suffered from hydrocephalus. However, nine of 17 patients (53%) were obese, a percentage that does not differ from the general German population (56%) [30]. Furthermore, we did not find any BMI differences between our two cohorts. Assuming a correlation or even causal connection between TE and obesity, a higher incidence of obesity would have been postulated in the BTE cohort.

Interestingly, we detected epilepsy characteristic differences between our two cohorts. One important aetiological finding is the age at epilepsy onset. Median age of onset was well within adulthood and earlier in UTE- vs. BTE groups (37 vs. 51 years). Although we did not find clear differences in suspected TE aetiology between the two cohorts, the age of onset analysis suggests that encephaloceles are, at least in part, an acquired entity. No positive family history for epilepsy could be identified in our study population, although images of relatives were not available. Consequently, there was no information about 'silent' TE in relatives. To date, to our knowledge, no data exist focusing on familial clusters of TE that would suggest a hereditary or genetic pathogenesis.

Although the average number of anticonvulsive medications did not differ between our two cohorts, our data illustrate that the risk of a drug-refractory course was much higher in BTE-associated epilepsy (71%) as compared to patients with UTE-associated epilepsy (50%). We assume, that the risk to suffer from a medication-refractory-epilepsy rises with the number of potentially epileptogenic lesions. This is relevant for further management, which might include surgical intervention. If bilateral, potentially epileptogenic lesions are found on MRI, video-EEG analysis is crucial to define the laterality and localisation of the epileptogenic zone (EZ) and define whether a unilateral EZ exists. If necessary, invasive EEG analysis has to be performed to evaluate tailored surgical options to achieve seizure freedom. In our sample, both patients with BTE-associated epilepsy who underwent a surgical intervention became seizure free. Nevertheless, the remaining contralateral encephalocele is a potential epileptogenic lesion and potential cause for ongoing seizures after surgical treatment [10]. As only two patients of our sample underwent a surgical treatment (temporal lobe resection on the right side including the hippocampus vs. temporal pole resection on the left side excluding the hippocampus), the cohort is too small to evaluate the best surgical intervention for patients suffering from TE-associated epilepsy.

Other questions are why and how TE causes epilepsy. Possible mechanisms include irritation of the cortical neurons due to herniation into a bony defect and dysplastic cortical lesions as part of a more complex malformation of the brain-skull base junction. Larger case series presented patients undergoing surgery, who had heterotopic neurons or focal cortical dysplasia of the resected parenchyma on histopathology [5,10,16,17], which may be the underlying epilepsy cause. In our study population, both patients who underwent resection of the temporal lobe showed gliosis only on histological analysis. Nonetheless, two other patients were identified to have amygdala enlargement compatible with an amygdala dysplasia by MRI findings. Although the

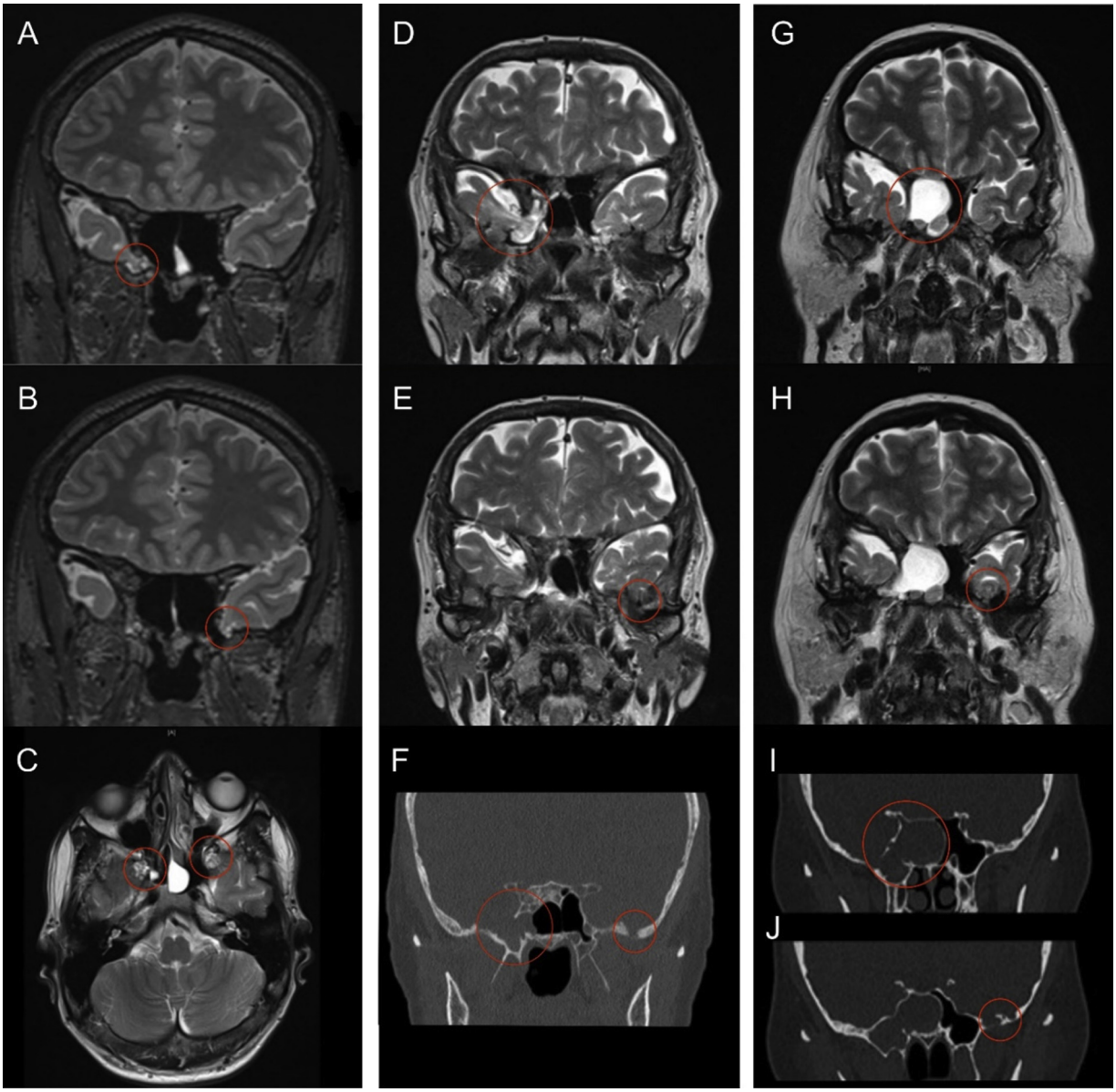

Fig. 2. Representive images of three patients with bilateral temporal encephalocele. Image A and B show coronal T2-spc-weighted sequence of 3 T MRI; Image C shows axial T2-weighted sequence of 3 T MRI; Images D/E/G/H show coronal T2-weighted sequence of 3 T MRI; Images F/I/J show coronal CT of the refering bony defect of the skull base. Lesions are circumscribed by a red circle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

MRI-based diagnosis of amygdala dysplasia is still challenging, our findings are consistent with the frequently reported coincidence of cortical dysplasia or heterotopia with TE. While this coincidence is unlikely to be explained by chance, a causative correlation between TE and cortical dysplasia as well as heterotopies must be scrutinised in further studies [31]. At this point, we want to clarify, that the enitity of amygdala dysplasia is still discussed controversially. It must be taken into account, that the MRI finding of an amygdala enlargement is not necessariliy due to a dysplasia as it can be related to seizures itself as well as to an immunomediated process (e. g. limbic enzephalitis).

This study suffers from certain limitations, which may have influenced the results. As a monocentre trial, local characteristics could have led to a systematic bias. A larger, multicenter cohort might be needed in order to conform this preliminary data. However, the comparability of our results with other case series suggest only minimal, if any, regional bias [5,10,15–17]. To reduce frequently associated methodical biases of retrospective studies STROBE and RECORD guidelines were followed [18–20]. All imaging findings were independently confirmed by an experienced neuroradiologist to minimise the likelihood of false positive findings. Together, these measures should reduce possible methodical limitations.

To facilitate knowledge acquisition on the clinical characteristics and pathophysiology of BTE- and UTE-associated epilepsy, we recently founded the TE-associated epilepsy consortium, which aims to accumulate a large patient cohort. The input of other groups is welcome (http://www.uni-frankfurt.de/67689811).

5. Conclusion

In this retrospective study, we show relevant differences between patients with BTE-associated epilepsy and UTE-associated epilepsy. BTE-associated epilepsy is characterised by higher age at epilepsy onset, shorter delay in TE diagnosis and more frequent drug resistance as compared to UTE-associated epilepsy. A standardised diagnostic

workup based on the awareness of TE and including high-resolution MRI and skull base CT, video-EEG monitoring and interdisciplinary decision making about therapeutic options is recommended to allow the best medical treatment for each patient. Further studies are needed clarifying the pathophysiology and clinical aspects of TE and to determine its role in structural epilepsy. Finally, as TE-associated epilepsy is still an underdiagnosed entity, multicentre studies will help answer important questions about disease incidence and prognosis.

Conflict of interest

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

E. Paule and T. Freiman have nothing to disclose.

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Authors contribution

FR and EP planned and designed the study. MW analysed all imaging-data. EP collected and interpreted the data and wrote the article. LMW created the charts. TMF performed the epilepsy surgery, TMF AS, PSR, MW, LMW, JPZ and FR made critical revisions. All authors approved the final manuscript.

References

[1] Wind JJ, Caputy AJ, Roberti F. Spontaneous encephaloceles of the temporal lobe. Neurosurg Focus 2008;25:E11.

[2] Byrne RW, Smith AP, Roh D, Kanner A. Occult middle fossa encephaloceles in patients with temporal lobe epilepsy. World Neurosurg 2010;73:541–6.

[3] Flugel D, Ostertun B, Bauer J, van Roost D, Elger CE. Iatrogenic brain prolapse: a rare complication of invasive presurgical evaluation of epilepsy. Neurology 1997;48:785–6.

[4] Mandl ES, Buis DR, Heimans JJ, Peerdeman SM. Acquired encephaloceles and epilepsy in osteopetrosis. Acta Neurochir (Wien) 2007;149:79–81. discussion 81.

[5] Urbach H, Jamneala G, Mader I, Egger K, Yang S, Altenmuller D. Temporal lobe epilepsy due to meningoencephaloceles into the greater sphenoid wing: a consequence of idiopathic intracranial hypertension? Neuroradiology 2018;60:51–60.

[6] Morone PJ, Sweeney AD, Carlson ML, Neimat JS, Weaver KD, Abou-Khalil BW, Arain AM, Singh P, Wanna GB. Temporal lobe encephaloceles: a potentially curable cause of seizures. Otol Neurotol 2015;36:1439–42.

[7] Magliulo G, Terranova G, Cristofari P, Petti R. Encephalocele with spontaneous CSF otorrhea. An Otorrinolaringol Ibero Am 1998;25:57–63.

[8] Kohrmann M, Schellinger PD, Wetter A, Hahnel S. Nasal meningoencephalocele, an unusual cause for recurrent meningitis. Case report and review of the literature. J Neurol 2007;254:259–60.

[9] Fountas KN, Smith JR, Jenkins PD, Murro AM. Spontaneous motor cortex encephalocele presenting with simple partial seizures and progressive hemiparesis. Case report and review of the literature. Neurosurg Focus 2005;19:E10.

[10] Saavalainen T, Jutila L, Mervaala E, Kalviainen R, Vanninen R, Immonen A. Temporal anteroinferior encephalocele: an underrecognized etiology of temporal lobe epilepsy? Neurology 2015;85:1467–74.

[11] Faulkner HJ, Sandeman DR, Love S, Likeman MJ, Nunez DA, Lhatoo SD. Epilepsy surgery for refractory epilepsy due to encephalocele: a case report and review of the literature. Epileptic Disord 2010;12:160–6.

[12] Aquilina K, Clarke DF, Wheless JW, Boop FA. Microencephaloceles: another dual pathology of intractable temporal lobe epilepsy in childhood. J Neurosurg Pediatr 2010;5:360–4.

[13] Shimada S, Kunii N, Kawai K, Usami K, Matsuo T, Uno T, Koizumi T, Saito N. Spontaneous temporal pole encephalocele presenting with epilepsy: report of two cases. World Neurosurg 2015;84(867):e861–6.

[14] Abou-Hamden A, Lau M, Fabinyi G, Berkovic SF, Jackson GD, Mitchell LA, Kalnins R, Fitt G, Archer JS. Small temporal pole encephaloceles: a treatable cause of "lesion negative" temporal lobe epilepsy. Epilepsia 2010;51:2199–202.

[15] Campbell ZM, Hyer JM, Lauzon S, Bonilha L, Spampinato MV, Yazdani M. Detection and characteristics of temporal encephaloceles in patients with refractory epilepsy. AJNR Am J Neuroradiol 2018;39:1468–72.

[16] Toledano R, Jimenez-Huete A, Campo P, Poch C, Garcia-Morales I, Gomez Angulo JC, Coras R, Blumcke I, Alvarez-Linera J, Gil-Nagel A. Small temporal pole encephalocele: a hidden cause of "normal" MRI temporal lobe epilepsy. Epilepsia 2016;57:841–51.

[17] Panov F, Li Y, Chang EF, Knowlton R, Cornes SB. Epilepsy with temporal encephalocele: characteristics of electrocorticography and surgical outcome. Epilepsia 2016;57:e33–8.

[18] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014;12:1495–9.

[19] Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sorensen HT, von Elm E, Langan SM, Committee RW. The REporting of studies conducted using Observational Routinely-collected health data (RECORD) statement. PLoS Med 2015;12:e1001885.

[20] Nicholls SG, Quach P, von Elm E, Guttmann A, Moher D, Petersen I, Sorensen HT, Smeeth L, Langan SM, Benchimol EI. The REporting of studies conducted using observational routinely-collected health data (RECORD) statement: methods for arriving at consensus and developing reporting guidelines. PLoS One 2015;10:e0125620.

[21] Rosenow F, Bast T, Czech T, Feucht M, Hans VH, Helmstaedter C, Huppertz HJ, Noachtar S, Oltmanns F, Polster T, Seeck M, Trinka E, Wagner K, Strzelczyk A. Revised version of quality guidelines for presurgical epilepsy evaluation and surgical epilepsy therapy issued by the Austrian, German, and Swiss working group on presurgical epilepsy diagnosis and operative epilepsy treatment. Epilepsia 2016;57:1215–20.

[22] Bundesverband A. Zahlen und Fakten 2014, Berlin, Germany, September. 2014.

[23] Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, Lagae L, Moshe SL, Peltola J, Roulet Perez E, Scheffer IE, Zuberi SM. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE commission for classification and terminology. Epilepsia 2017;58:522–30.

[24] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshe SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069–77.

[25] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshe SL, Nordli DR, Perucca E, Tomson T, Wiebe S, Zhang YH, Zuberi SM. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia 2017;58:512–21.

[26] Luders HO, Amina S, Baumgartner C, Benbadis S, Bermeo-Ovalle A, Devereaux M, Diehl B, Edwards J, Baca-Vaca GF, Hamer H, Ikeda A, Kaiboriboon K, Kellinghaus C, Koubeissi M, Lardizabal D, Lhatoo S, Luders J, Mani J, Mayor LC, Miller J, Noachtar S, Pestana E, Rosenow F, Sakamoto A, Shahid A, Steinhoff BJ, Syed T, Tanner A, Tsuji S. Modern technology calls for a modern approach to classification of epileptic seizures and the epilepsies. Epilepsia 2012;53:405–11.

[27] Loddenkemper T, Kotagal P. Lateralizing signs during seizures in focal epilepsy. Epilepsy Behav 2005;7:1–17.

[28] Lueders HO, Award, I.A. Conceptual considerations. In: Lueders H, editor. Epilepsy surgery. New York: Raven Press; 1992.

[29] Webb AJ, Ullman NL, Morgan TC, Muschelli J, Kornbluth J, Awad IA, et al. Accuracy of the ABC/2 score for intracerebral hemorrhage: systematic review and analysis of MISTIE, CLEAR-IVH, and CLEAR III. Stroke 2015;46:2470–6.

[30] DiBonaventura M, Nicolucci A, Meincke H, Le Lay A, Fournier J. Obesity in Germany and Italy: prevalence, comorbidities, and associations with patient outcomes. Clinicoecon Outcomes Res 2018;10:457–75.

[31] Malter MP, Widman G, Galldiks N, Stoecker W, Helmstaedter C, Elger CE, et al. Suspected new-onset autoimmune temporal lobe epilepsy with amygdala enlargement. Epilepsia 2016;57:1485–94.