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# Transient epileptic amnesia is significantly associated with discrete CA1-located hippocampal calcifications but not with atrophic changes on brain imaging

Running title: Brain imaging in transient epileptic amnesia.

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## Abstract

*Background:* The exact etiology of transient epileptic amnesia (TEA) is currently unknown. In older individuals, common neurodegenerative dementias and small-vessel diseases (SVDs) could be major contributors. We examined these hypotheses on the basis of imaging analysis.

*Methods:* In total, 36 TEA patients were compared with 25 healthy controls for (1) cortical atrophic changes (in the mesial temporal, frontal, anterior temporal, and parietal regions) using four established MRI-based visual rating scales, and for (2) SVD evidence using two MRI-based visual rating scales (Fazekas and MARS scores). In 24 TEAs cases, there were also brain CT scans available that were compared with 57 controls for the presence of hippocampal calcifications (HCs).

*Results:* We did not find significant differences in cortical atrophy between TEAs and controls, nor did we observe a different SVD brain load on MRI. However, TEAs were significantly associated ( $p < 0.01$ ) with uni- or bilateral CA1-located HCs in half of the patients compared with the controls (less than 20%).

*Conclusions:* This study argues in favor of a hippocampal-restricted SVD (as indicated by HCs) as one of the major etiologies of TEA, while neurodegenerative dementias are probably minor causes. It furthermore highlights the pivotal role of the CA1 hippocampal subfield in the pathophysiology of this syndrome.

## Introduction

Transient epileptic amnesia (TEA) has now been thoroughly characterized based on publications dating back to the 1990s [1,2] supplemented by two important articles in the 2000s and 2010s [3,4]. It has been established that this syndrome of late-onset temporal lobe epilepsy (commonly starting after the age of 50 years) manifests both by transient, repeated acute memory disturbances (amnesic seizures strictly speaking) and by interictal and therefore chronic memory disorders (i.e., accelerated forgetting, autobiographical amnesia, and topographical amnesia). The latter suggest permanent mesial temporal dysfunction, predominating in the hippocampus [5]. In fact, volumetric studies have shown decreased volume in both hippocampi of TEA patients, correlated with performance on standard memory tests but not with accelerated forgetting or with autobiographical memory evaluations and therefore with subjective complaints [6]. The major etiology of TEA is unknown, but all conditions involving the mesial temporal lobe regions – in particular the hippocampus – are potential causes, which include neurodegenerative diseases. Several case reports consistently showed that Alzheimer's disease [7], frontotemporal dementia [8], and even Lewy body disease [9] may trigger TEA. Yet, they are probably not representative because this epilepsy syndrome has a low risk of conversion to dementia, contrary to the natural history of neurodegenerative disorders [10,11]. Moreover, the vascular origin – especially the involvement of cerebral small-vessel diseases (SVDs) – has been suspected since the publication by Zeman *et al.* [2] but was not confirmed in a subsequent study [12]. This may be due to the use of inappropriate SVD imaging markers (Fazekas or Wahlund scores measuring white matter changes), since they are measured outside the mesial temporal lobe regions that are central to TEA pathophysiology [13]. By contrast, CT scan-visible hippocampal calcifications (HCs) open up an interesting perspective: they most likely indicate a specific SVD of the hippocampus because their vascular origin is neuropathologically proven [14], since they are linked to the presence of vascular risk factors such as diabetes and smoking [15] as well as to mild-to-moderate cognitive impairment [16-18]. HCs could therefore be a relevant SVD feature in TEA. In view of the scarce data in the literature regarding

potential neurodegeneration and/or SVD-related TEAs, we examined whether there was evidence for such etiologies on imaging (including HCs) in a retrospective cohort.

## Patients and methods

### Selection of patients and TEA characterization

*Patient selection.* In January 2018, we searched the database of the Memory Clinic (Strasbourg University Hospital) for patients who had been diagnosed with transient amnesic syndromes from 2012 to 2016 ( $n=320$ ). Among these patients, we then searched for patients who had been diagnosed with TEA according to current criteria [2]: (1) recurrent, witnessed episodes of unprovoked transient amnesia (at least two as defined by the current epilepsy guidelines); (2) cognitive functions other than memory judged to be intact by a reliable witness during the attack; (3) evidence for a diagnosis of epilepsy based on one or more of: epileptiform EEG abnormalities, co-occurrence of other clinical features of epilepsy (e.g., automatisms, olfactory hallucinations), and a clear-cut response to antiseizure medications (ASMs). For patients who had only one occurrence of clinically typical TEA (i.e., short duration, upon waking), epileptiform discharges and/or accompanying epileptic features were mandatory for the diagnosis (supplemental table 1). A total of 67 individuals met the TEA criteria. The mandatory inclusion criteria for this study were: (1) having undergone a brain MRI within 1 year of diagnosis, or before (since seizure onset), which (2) included at least longitudinal FLAIR, coronal T1-weighted reconstructions, and longitudinal T2-weighted gradient-echo and/or susceptibility-weighted imaging (SWI) acquisitions (Figure 1). The exclusion criteria were: a clinical dementia rating scale score  $> 0.5$ ; insufficient clinical and/or EEG documentation at baseline; insufficient follow-up to ensure seizure response to ASM ( $< 2$  years); loss follow-up ; incomplete/unavailable MRI data or MRI performed more than 1 year after the diagnosis; or a prior history of epileptic seizures, alcohol or drug abuse, Korsakoff syndrome, uncontrolled severe medical disease (including extraneurologic primitive cancers, HIV or Lyme infection, congestive heart failure, uremia, hypercalcemia, hyponatremia), untreated endocrinal disturbances or B-vitamin deficiency, multiple sclerosis or other demyelinating diseases, cortical

stroke, brain tumors, neurosurgery or severe traumatic brain injury with cerebral contusion and/or hematoma. Finally, 36 individuals were included in the study, six of whom (16.7%) had only one occurrence of TEA. In the end, we identified 24 patients with available brain CT scans that were carried out before being referred to our Memory Clinic. Examinations were performed within the year of diagnosis or before, since the onset of seizures, for the diagnostic work-up of unexplained transient amnesia(s).

**\*\* Insert figure 1 \*\***

*TEA characterization.* The age at epilepsy diagnosis was retained as the age of ASM prescription or, if not, as the age of the epileptiform EEG recording. The characteristics of the TEAs were taken from structured interviews with the patients themselves and their caregiver(s): age of first occurrence, precipitants, occurrence on waking, number of iterations with their duration in minutes and their frequency, accompanying ictal signs (i.e., brief contact loss, automatisms, olfactory hallucinations, etc.), repetitive questioning, anterograde and/or retrograde amnesia during spells, and partial recall of the amnestic attack.

*Electroencephalogram (EEG).* Standard and/or video-electroencephalography was performed for each patient, with the international 10–20 system for scalp electrodes in a session lasting at least 30 min. On EEGs, epileptic foci were defined as the regions of maximum electronegativity. Nonepileptiform recordings included background slowing in the theta and/or delta range. Epileptiform recordings were defined by seizures and/or interictal epileptiform discharges (IEDs; sharp waves and/or spikes and/or spike waves). No sleep-deprived EEGs were performed.

*Antiseizure medications.* All patients were proposed an ASM when the diagnosis of epilepsy was retained, based on clinical  $\pm$  electrical features. All but two (5.5%) patients accepted it. The choice of the drug was made by the patient's referring physician. We recorded the drug type and the daily dosage of the prescribed ASM. The clinical response was measured in the patient's and caregiver's diary. Seizure response was defined as a reduction in seizure frequency of > 50%.

*Clinical and paraclinical measures.* All patients underwent Mini-Mental State Exam (MMSE) scoring at baseline. The other medical features were obtained from patients and caregivers: demographics, education and professional occupation, personal and family medical history, age of onset, and type of cognitive changes (with special attention paid to accelerated forgetting, topographical amnesia, and autobiographical memory deficits). All patients underwent physical examination as well as dementia blood screening (including B<sub>12</sub> and folates).

## Selection of controls

*MRI healthy controls.* Healthy volunteers for brain MRI protocols were recruited via advertisements in local community newsletters in Strasbourg (they contacted our Memory Clinic after reading the announcements that we were seeking controls for clinical studies) and via the listing of controls at the local clinical investigation center (*Centre d'Investigation Clinique*) in charge of all types of medical research conducted at the Strasbourg University Hospital. All enrolled participants were verified as being cognitively healthy on the basis of normal neuropsychological test results (global CDR score = 0, MMSE score > 24, Frontal assessment battery score ≥ 16, normal results on subtests exploring memory, executive functions, verbal fluencies, gestural praxic abilities, attentional and visuoconstructive abilities) and were judged to be neurologically healthy on the basis of normal clinical examination and normal scale scores (UPDRS III score ≤ 3, fluctuations scale score = 0). Twenty-five healthy controls matching our patients for age and gender were included. MRI sequences included longitudinal FLAIR, longitudinal T2-weighted gradient-echo and longitudinal millimetric MPRAGE. The latter provides a 3D reconstruction for the rating of the different atrophy scores used in this study (see below). The results of the MRI scans were registered in the database of the IMIS-ICube Laboratory initially created for the alpha-Lewy-MA study [19].

*CT scan control group.* Patients were identified from the database of the Neuroradiology Department of the Strasbourg University Hospital. The list of all the consecutive patients who had undergone a brain CT between December 2019 and June 2020 was extracted. We excluded patients with abnormal brain CT scans and, if normal, patients with a prior or ongoing chronic neurological



condition according to the medical records (including dementing diseases). Patients matching the TEA individuals for age and gender were then selected ( $n=57$ ). Indications for CT were, in descending order: head trauma (44 [77.2%]), iatrogenic confusion (7 [12.3%]), headache (5 [8.8%]), fall while on a vitamin K antagonist (1 [1.7%]).

## Imaging ratings

On MRI, six quantitative visual rating scales were used. They explored atrophic changes (on coronal reconstructions) and SVDs (on longitudinal appropriate sequences). First, mesial temporal lobe atrophy (reflecting hippocampal volume) was staged with the Scheltens visual scale ranging from 0 (no atrophy) to 4 (maximum atrophy) [20]. Second and third, frontal and anterior temporal lobe atrophy was assessed with the Kipps visual scale, ranging from 0 (no atrophy) to 4 (maximum atrophy) [21]. Fourth, parietal atrophy was staged with the Koedam visual scale, ranging from 0 (no atrophy) to 3 (maximum atrophy) [22]. Fifth and sixth, white matter hyperintensities were staged with the Fazekas visual scale, ranging from 0 (no hyperintensities) to 3 (confluent extensive hyperintensities) [23]; and microbleeds with the MARS score, reflecting the sum of lesions seen in anterior and posterior fossa [24]. On available CT scans, three qualitative measurements were given for hippocampal calcifications (HCs): no visually detectable HCs, unilateral (right or left) HCs, or bilateral (right and left) HCs. The MRIs and CT-scans of patients and controls were independently rated by two trained neurologists (rater #1 = AB, rater #2 = BC). They were not blinded to the diagnosis (patient vs. control) but were not aware of the other rater's ratings. After completion of their independent report, they compared their results. Each rater had a total of 216 MRI-based scores for patients (i.e., six different scores established on 36 available MRIs) vs. 150 for controls (i.e.,  $6 \times 25$ ), and a total of 72 CT-based scores for patients (i.e.,  $3 \times 24$ ) vs. 171 for controls ( $3 \times 57$ ).

## Statistical analysis

Quantitative variables are described using standard position and dispersion statistics, namely, mean, median, variance, minimum, maximum, and quantiles. Qualitative variables are described with the numbers and proportions of each category. Cumulative proportions were also

calculated for variables with more than two categories. The Gaussian character of the quantitative variables was evaluated using the Shapiro–Wilk test. We used the nonparametric Mann–Whitney  $U$  test, or Student  $t$  test as appropriate, to test differences in means (or other quantitative variables) between groups, and Fischer's exact test, or the chi-square test as appropriate, to compare two sample proportions (%). Rater agreement on imaging was determined using the Spearman coefficient for quantitative scores (i.e., measurements of cortical atrophy, white matter hyperintensities, and microbleeds) and using Cohen's kappa for qualitative measurements (i.e., presence or absence of hippocampal calcifications). All analyses were performed using the R software version 3.1 (R development Core Team, 2008), via the Strasbourg University Hospitals' GMRC Shiny Stats software (2017).

#### Standard protocol approval, registration, and patient consent

All retrospective study procedures were performed following protocols approved by the Institutional Review Board (*Direction de la Recherche Clinique et de l'Innovation*) at our center. Written informed consent was obtained from all research participants recruited. The study was conducted in accordance with the Declaration of Helsinki.

#### Data availability

Data that support the findings of this study are available from the corresponding author upon reasonable request.

## Results

### Clinical characteristics of TEA patients

The main clinical features of the 36 patients are displayed in **Table 1**. The complaint of amnesia was very common, mainly consisting in accelerated forgetting. It started at a mean age of 66 years, which was usually concomitant with seizure onset or soon after (within less than 1 year).

**Table 1: Clinical features of the cohort**

TEA ( $n=36$ )	
Demographics	

Women, <i>n</i> (%)	26 (72)
Education, years, mean ( $\pm$ SD)	11.2 (2.3)
Handedness (R/L), %	97.2/2.8
Age at cognitive complaints, years, mean ( $\pm$ SD)	66.0 (9.0)
Age at MRI acquisition, years, mean ( $\pm$ SD)	70.4 (8.4)
Age at CT scan acquisition, years, mean ( $\pm$ SD)	71.8 (7.5)
<b>Cognitive complaints, <i>n</i> (%)</b>	
Accelerated forgetting	31 (87)
Autobiographical amnesia	11 (30)
Topographical amnesia	17 (47)
<b>Baseline MMSE score, mean (<math>\pm</math> SD)</b>	<b>26.9 (2.5)</b>
<b>Cardiovascular risk factors, <i>n</i> (%)</b>	
Hypertension	17 (47.2)
Diabetes mellitus	3 (8.3)
Dyslipidemia	14 (38.9)
Smoking (active or discontinued)	6 (16.6)
Alcohol consumption	3 (16.6)
Cardiac disease	9 (25)

### Epileptological features of TEA patients

The epileptological features of the TEA patients are summarized in **Table 2**. The mean age at onset of amnesic seizures was 65.2 years, while the mean age at diagnosis was 69.1 years. Prior to the diagnosis, patients had a median 4.5 acute amnesic episodes, commonly lasting between 12 and 60 min; **but 6 (16.7%) had only one occurrence of TEA (Supplemental Table 1)**. 34 were treated with ASM monotherapy, including 29 (85.3%) with lamotrigine (mean daily dose = 164 mg  $\pm$  114). Of the treated patients, 64.7% were seizure-free (no relapse of acute amnesia) and 35.3% were not seizure-free but responders (decrease in seizure frequency  $\geq$  50%). Only one (2.9%) did not respond. Regarding interictal chronic memory complaints, 17 (50%) reported subjective relief under ASM therapy.

**Table 2: Epileptological features of the cohort**

	TEA ( <i>n</i> =36)
<b>Age at first seizure, years, mean (<math>\pm</math> SD)</b>	<b>65.3 (8.6)</b>
<b>Age at epilepsy diagnosis, years, mean (<math>\pm</math> SD)</b>	<b>69.1 (9.3)</b>
<b>Seizure semiology</b>	

Iterations, median (min–max)	4.5 (1–200)
Maximum duration, min, median (min–max)	60 (3–1440)
Minimum duration, min, median (min–max)	12.5 (0.5–1440)
Ictal anterograde amnesia, <i>n</i> (%)	30 (83)
Ictal retrograde amnesia, <i>n</i> (%)	31 (87)
Repetitive questioning, <i>n</i> (%)	12 (33)
Upon waking, <i>n</i> (%)	7 (19)
Accompanying epileptic signs, <i>n</i> (%)	30 (83)
<b>EEG features, <i>n</i> (%)</b>	
First standard EEG	Normal: 22 (65) Slowing: 9 (26.5) Right: 3 (8.8) Left: 5 (14.7) Bilateral: 1 (3) IEDs: 3 (9) Left: 2 (6) Bilateral: 1 (3) Seizure: 0 Not done: 2 (6)
Video-EEG	Normal: 7 (25) Slowing: 8 (28.5) Left: 4 (14.25) Bilateral: 4 (14.25) IEDs: 11 (39) Right: 1 (4) Left: 4 (14) Bilateral: 6 (21) Seizure: 2 (7) Left: 2 (7) Not done: 8 (22)

#### Atrophy scores and small-vessel disease evidence on brain MRI

The mean scores, calculated from the pooled results of both raters, for TEA patients and for MRI controls, are presented in **Table 3**. There was no statistically significant difference between TEA patients and controls for atrophy or SVD brain load (as evidenced by the Fazekas and MARS scores). HCs were not visible on MRI using T2-weighted gradient-echo or SWI acquisitions because of technical limitations (thick slices). The MRI control participants were significantly more educated and had a higher MMSE score than the TEA patients ( $p = 0.02$  and  $0.01$ , respectively).

**Table 3: Mean scores of atrophic and vascular changes of patients and healthy controls**

	TEA ( <i>n</i> =36)	MRI controls ( <i>n</i> =25)	<i>p</i>
<b>Female, <i>n</i> (%)</b>	26 (72)	14 (63.6)	0.4
<b>Education, years, mean (<math>\pm</math> SD)</b>	11.4 (2.4)	12.8 (2.7)	<b>0.02</b>

MMSE score	26.9 (2.5)	28.8 (0.9)	<b>0.01</b>
Age at MRI acquisition, years, mean ( $\pm$ SD)	70.4 (8.8)	67.2 (8.5)	0.4
Right MTA, mean ( $\pm$ SD)	1.2 (0.8)	1.2 (1)	0.9
Left MTA, mean ( $\pm$ SD)	1.2 (0.8)	1.2 (0.9)	0.8
Right frontal lobe atrophy, mean ( $\pm$ SD)	0.8 (0.7)	0.7 (0.8)	0.6
Left frontal lobe atrophy, mean ( $\pm$ SD)	0.8 (0.7)	0.75 (0.8)	0.7
Right anterior temporal lobe atrophy, mean ( $\pm$ SD)	0.7 (0.7)	0.5 (0.5)	0.3
Left anterior temporal lobe atrophy, mean ( $\pm$ SD)	0.8 (0.7)	0.7 (0.6)	0.3
Right parietal lobe atrophy, mean ( $\pm$ SD)	1.0 (0.8)	1.2 (0.9)	0.3
Left parietal lobe atrophy, mean ( $\pm$ SD)	1.0 (0.8)	1.3 (0.9)	0.1
Fazekas score, mean ( $\pm$ SD)	1.2 (0.9)	1.0 (0.7)	0.3
MARS lobar score, mean ( $\pm$ SD)	0.3 (0.7)	0.1 (0.4)	0.1
MARS deep score, mean ( $\pm$ SD)	0.4 (1.1)	0.3 (0.5)	0.4

Note: The posterior temporal lobe atrophy scores were not measured because the anterior temporal lobe atrophy scores were preferred given their relevance for TDP-43-related neurodegenerative changes mainly affecting the temporal poles; the MARS score for the infratentorial structures and the cerebellum was not measured given these structures' low relevance for epilepsy, which involves distant cortical structures; MTA, mesial temporal lobe atrophy.

#### Hippocampal calcifications on CT scans

The separate comparisons between TEAs and CT controls of rater #1 and #2 are presented in **Table 4**. They both found a significant association of HCs, uni- or bilateral, with TEAs ( $p < 0.01$  or  $p < 0.001$  for rater #1 and #2, respectively). There was a clear predominance of HCs on the right hemisphere. All patients with HCs were right-handed. The comparison between HC-positive and HC-negative patients was made for each rater: No significant difference was found for demographic, clinical (including cardiovascular risk factors), epileptological, cognitive, and radiological data (not shown). This includes the progression of the cognitive complaint under ASM (e.g., for rater #2, the cognitive complaint was improved for 7/12 [58.3%] of the HC-negative and for 5/12 [41.7%] of the HC-positive patients,  $p = 0.41$ ). Right or left HCs did not correlate with a specific cognitive complaint **nor they did with the epileptic focus on EEG** (not shown). Examples of bilateral HCs are given in Figure 2.

210 **Table 4: Compared prevalence of HCs in TEA patients and controls according to both raters.**

		TEA ( <i>n</i> =24)	CT scans controls ( <i>n</i> = 57)	<i>p</i> (TEA vs. controls)
<b>Female, <i>n</i> (%)</b>	-	26 (72)	40 (70.2)	0.8
<b>Education, years, mean (<math>\pm</math> SD)</b>	-	11.4 (2.4)	NA	-
<b>MMSE score</b>	-	26.9 (2.5)	NA	-
<b>Age at CT scan acquisition, years, mean (<math>\pm</math> SD)</b>	-	71.8 (7.5)	69.2 (5.2)	0.1
<b>Age at diagnosis in patients with available CT scan</b>		72.5 (7.8)	-	-
<b>Right hippocampal calcifications, <i>n</i> (%)</b>	Rater #1	11 (45.8)	5 (8.8)	<b>&lt; 0.001</b>
	Rater #2	12 (50)	6 (10.5)	<b>&lt; 0.001</b>
	Interrater agreement	$\kappa = 0.9^{\dagger}$	$\kappa = 0.5^{\dagger}$	-
<b>Left hippocampal calcifications, <i>n</i> (%)</b>	Rater #1	6 (25)	7 (12.3)	0.2
	Rater #2	6 (25)	4 (7.0)	0.06
	Interrater agreement	$\kappa = 1^{\dagger}$	$\kappa = 0.7^{\dagger}$	-
<b>Right and/or left hippocampal calcifications, <i>n</i> (%)</b>	Rater #1	12 (50)	10 (17.5)	<b>0.01</b>
	Rater #2	12 (50)	7 (12.3)	<b>&lt; 0.001</b>
	Interrater agreement	$\kappa = 1^{\dagger}$	$\kappa = 0.7^{\dagger}$	-

211 Note: Rater # 1 = AB, rater #2 = BC;  $^{\dagger} = p < 0.001$  for agreement between rater #1 and rater #2 according to Cohen's kappa coefficient

212 \*\* Insert Figure 2 \*\*

### 213 Rater agreement

214 Qualitative measures of HCs were significantly correlated with Cohen's kappa, ranging from  
215 0.5 to 0.9 for right HCs ( $p < 0.001$ ) and from 0.7 to 1.0 for left HCs ( $p < 0.001$ ) (Table 3), with a  
216 moderate ( $\kappa = 0.5$ ) to strong ( $\kappa = 1$ ) agreement according to Landis and Koch. Interrater agreement  
217 was good for quantitative atrophy scores with a statistically significant correlation coefficient  
218 between raters for all measurements (Spearman rho,  $p < 0.01$ ), ranging from 0.7 to 1.0 for mesial  
219 temporal lobe atrophy scores, from 0.6 to 0.8 for both frontal atrophy and anterior temporal lobe  
220 atrophy, and from 0.5 to 0.8 for parietal atrophy (Supplemental Table 2). MRI evidence of SVD was  
221 also significantly correlated between the two raters, with rho ranging from 0.75 to 0.9 for the  
222 Fazekas score ( $p < 0.001$ ), from 0.7 to 0.9 for the lobar MARS score ( $p < 0.001$ ), and 0.9 for the deep  
223 MARS score ( $p < 0.001$ ) (Supplemental Table 2).

## Discussion

### A large and representative cohort of TEA patients

This work describes the clinical, electrical, and radiological characteristics of 36 patients with TEA: they replicate the prior reported clinical and paraclinical features of TEA (except in terms of the female overrepresentation). It is one of the largest published cohorts since the studies reported by Butler *et al.* [3] and Mosbah *et al.* [4], which included 50 and 30 cases of TEAs, respectively. The other published studies were indeed smaller, including 19 [25], 15 [26], and 11 patients [27], as was the princeps case study by Zeman *et al.* ( $n = 10$ ) [2].

### The interictal cognitive complaints facilitate faster recognition of TEA

The present study highlights that the diagnosis of TEA is still delayed for several years (here nearly 4 years on average, similar to other studies) [4,25], but it can also be diagnosed on the first isolated amnesic transient, as it was the case in 6 (16.7%) patients based on electro-clinical features that were not consistent with the diagnosis of TGA and that moreover fitted with the ILAE definition of epilepsy (see Supplemental table 1) [26-28]. Amnesic attacks are in fact poorly understood during their initial management [3,4,26]. There are frequent relapses (mean,  $18 \pm 35$  occurrences here), as Butler *et al.* reported ( $18 \pm 17$  occurrences), but the median total number of attacks for our patients was significantly lower than that published by the same authors (4.5 vs. 10 total iterations) [3]. This indicates that TEAs are currently being recognized more quickly, probably because specific interictal memory deficits are now taken into account [4,25,30,31]. Anterograde memory complaints were indeed more frequent in this study than in others: For example, 21% of patients complained of accelerated forgetting in one study [25], 44% in another [3], and 87% in the present cohort. This can be explained by two factors: (1) the recruitment procedures in a Memory Center, which are not exclusively based on transient acute amnesic spells (i.e., TEAs) but on chronic cognitive impairment as well; (2) the fact that we are especially attentive to patients' cognitive complaints for the diagnosis of TEA, particularly in the case of a first amnesic attack [30]. We believe that both these factors shortened the time to diagnosis. However, a retrospective bias is not excluded: patients who

initiated treatment and continued follow-up in our Memory Center were possibly more concerned about their memory than others, thus increasing the present prevalence of memory complaints.

#### [No evidence of neurodegenerative or classic small-vessel disease on MRI in TEA cases](#)

This study is the first to investigate the yield of MRI-based atrophy visual rating scales in TEA, while other imaging methods have already been addressed (i.e., volumetric MRI and PET scans) [4,6,25,32]. These scales have all been validated by appropriate studies and published in international scientific journals. They provide easy, quick, and reproducible measurements of atrophy in neurodegeneration-sensitive key regions of the brain [33]. They thus make it possible to argue for underlying incipient dementia in TEA, in particular when persistent cognitive complaints are present [7-9]. The good interrater agreement obtained here is in line with previous publications [20-22,33] and confirms the applicability of such scales to late-onset epilepsy syndrome. This study did not find any significant lobar atrophic changes in patients compared with healthy controls. This indirectly suggests that neurodegenerative dementias are infrequent in TEA, consistent with a previous publication [10]. Furthermore, this study did not find evidence of significant vascular changes in TEA based on MRI scores [13], confirming the findings of an earlier report [12]. However, the Fazekas and MARS scales are probably not relevant to this late-onset temporal lobe epilepsy, as stated in the Introduction, because they are measured in anatomical sites distant from the region of interest in TEA (i.e., the hippocampus) [4,6,25,34,35].

#### [Hippocampal calcifications indicate a hippocampal restricted SVD in a substantial proportion of TEA patients](#)

HCs are easily identified on CT scans (because of thin slices and high contrast), which is confirmed in the present study by the strong interrater agreement regarding their detection in TEA patients and controls. They are likely a marker of microvascular damage to the hippocampus given their intraparietal location in the hippocampal capillaries as well as in the hippocampal pre-capillaries and arterioles [14]. In addition, they correlate with cognition [15-17]. We show here that HCs and TEAs are significantly associated in comparison with controls. Uni- or bilateral HCs were present in half of the cases in this study ( $p < 0.01$ ) but were not combined with evidence of diffuse cerebral SVD



(see section above). In fact, if all of the unavailable CT scans ( $n = 12$ ) were normal, HCs would still affect one third of the patients (12/36); on the contrary, if they were all abnormal, HCs would be present in two thirds of TEA (24/36). As a consequence, HCs most probably indicate that a specific and limited hippocampal SVD is one of the major causes of TEA. This result is in accordance with previously published neuropathological TEA reports that showed intrahippocampal capillary calcifications [38,39]. It is also in line with numerous studies in older individuals indicating that vascular pathology is a major cause of epilepsy [36]. This includes cerebral SVD [37]. Furthermore, such limited hippocampal SVD would explain why TEA carries a low risk of conversion to dementia (including vascular dementia) [10].

#### Hippocampal calcifications probably play a role in the pathogenesis of ictal and interictal features of affected TEA patients

Beyond their etiological value, HCs also add pathophysiological information. When present, they are very likely to be involved in the pathogenesis of the clinical picture of affected TEA patients, whether in their transient amnesic attacks or in their interictal memory deficits. With regard to iterative acute transient amnesias, it should be noted first that SVDs are recognized as epileptogenic: by blood–brain barrier breakdown [40] and, in the case of HCs, by a probable loss of normal astrocyte function as well. The latter results from an ectopic osteogenic environment [41]. Second, HCs are preferentially located in the CA1 field of Ammon's horn [14]. The disorganization of this hippocampal subfield is crucial for the production of transient amnesia. This is demonstrated by the association of a CA1-located punctuate cytotoxic edema with the onset of benign transient global amnesia (TGA), which clinically resembles TEA but lasts longer [42]. In this perspective, very focal seizures arising in the immediate vicinity of the HCs – in the CA1 subfield – could explain an isolated (or predominant) ictal amnesic presentation even in the case of rapid spread to both hippocampal structures [34,43]. In addition, due to their preferential right hippocampal location (i.e., the nondominant hemisphere for all the HC-positive patients in this study), the HCs could cause seizures restricted to the nondominant temporal lobe regions, which are more frequently manifested by brief

auras followed by automatisms with preserved consciousness [44], i.e., causing seizures with clinical semiology similar to the TEA described in the literature and herein [1-4,25, 26, 29]. Such hypothesis cannot yet be affirmed given the lack of correlation between HCs lateralization and EEG foci. Further studies are needed on this point, with stronger statistical power (i.e. more patients with recorded epileptiform EEGs and more available CT-scans). Regarding the interictal chronic memory deficits, CA1-located HCs may again be explanatory. They may disrupt the mnemonic encoding and storage processes involving this part of the cornu ammonis [42,45] and consequently explain the chronic memory complaints of patients regarding episodic memory deficits (i.e., accelerated forgetting or autobiographical amnesia, which are probably interrelated) [46]. It is noteworthy that the key role played by CA1 in autobiographical memory has been demonstrated in patients with TGA as well [47]. Furthermore, the topographical amnesia reported by patients may also be based on disturbed CA1-located place cells [48]. Due to the design of the present study – lacking appropriate and comprehensive testing of accelerated forgetting, topographical and autobiographical amnesia – we cannot provide confirmatory correlations of HCs with such specific cognitive deficits. If present, they would have reinforced this discussion. Finally, HCs could also explain why patients on effective ASM therapy persistently complain of memory problems even though seizures and IEDs no longer appear on EEG recordings.

#### HC-negative TEA patients do not differ from HC-positives: a specific CA1 disturbance in all TEA patients?

Interestingly, we did not find statistical differences between HC-positive and HC-negative TEAs, nor we did find a significant effect of the lateralization of HCs on specific cognitive complaints. These results have limited relevance due to the small number of HC-positive patients. Nevertheless, they point to the chronic disturbance of bilateral CA1 subfields in all TEA cases, with or without colocalized HCs. Neuronal loss and gliosis have been described in neuropathological cases: They affected the CA1 subfield of the hippocampus and the other parts as well (CA1-4) [38,39,49,50]. Moreover, these changes have been previously linked to accelerated forgetting and autobiographical

amnesia in a case with pathological verification [39]. They may explain occasional MRI-apparent hippocampal atrophy or sclerosis [29]. CA1 chronic impairment therefore convincingly explains the ictal and interictal amnesic features, as well as the persisting memory deficits despite a well-conducted ASM therapy in patients with TEA. In other words, persistent bilateral CA1 disruption may be the common thread of the full-blown clinical picture. We now need to establish if it explains the subtle loss of hippocampal volume seen in TEA cases, with better correlations with cognition [6,32,39], and to understand the etiology of TEAs in HC-negative individuals.

### Study limitations

One of the major biases of this study is that the raters were not blinded to the diagnosis when analyzing MRI and CT acquisitions of patients and controls. They carried out their ratings independently, and they were well correlated, but a diagnostic bias may explain the agreement. Nevertheless, they both retrieved a proportion of HCs in controls similar to the general population [17,18]. This indirectly indicates that their estimation was quite accurate. In addition, our retrospective design entails missing data (in particular for CT scans, not systematically carried out at seizure onset) and probably accounts for the overrepresentation of women in this study, whereas TEA usually affects slightly more men than women [3,4]. Yet, a cohort with predominantly female representation has already been reported [26]. The present study also suffers from recruitment biases. First, the MRI controls were recruited via advertisements. This led to a selection bias that resulted in significantly higher educational levels and MMSE scores in healthy individuals. However, the difference in MMSE scores is not clinically relevant because patients and controls both had mean scores above the pathological cut-off ( $\text{MMSE} \geq 24$ ). Second, the CT scan controls were recruited only on the basis of their medical record without clinical verification of normal cognition and neurological status. The representativeness of the CT control group is therefore altered. The frequency of HCs in our control group was similar, however, to that found in the general population [17,18]. Finally, this study also has design limitations. Neurodegeneration was assessed using MRI atrophy scores, which correspond to the "N" marker in the A/T/N classification proposed by Jack *et al.* [51]. A more in-

depth evaluation of neurodegeneration in TEA should also take into account the A ( $\beta$ -amyloid) and T (Tau) markers of the same classification. In other words, studies examining the yield of CSF or molecular scintigraphy tracers (amyloid and/or Tau-PET scans) would better document a possible underlying incipient neurodegenerative disorder. In a similar perspective, SVD evidence on imaging may be explored not only with white matter hyperintensities and microbleeds but with subcortical lacunes, subcortical and cortical microinfarcts, and Virchow–Robin space enlargement [13].

## Conclusion

This study of representative TEAs did not show the involvement of brain atrophic changes: It therefore seems reasonable to consider dementias as minor etiologies of TEA [10]. By contrast, our results argue for SVD being a major cause of TEA as reflected by HCs on brain CT scans (present in at least one third of the patients, but their exact prevalence now needs to be determined). HCs most likely reflect vascular damage restricted to the hippocampus. By extension, HCs indicate that the TEA features, whether ictal or interictal, are related to limited alterations in Ammon’s horn (i.e., CA1 subfield at least). This postulate needs to be confirmed by further studies, at least exploring correlations of HCs with detailed and specific cognitive paradigms. Specific MRI protocols (7T, quantitative susceptibility mapping, spectroscopy) may also be contributive.

## Author contributions

BC and AB contributed to the study design. AB, BC, NP, FB and FS contributed in the production of the main text of the manuscript. BC supervised data acquisition, and revised the manuscript. BC and AB performed statistical analysis.

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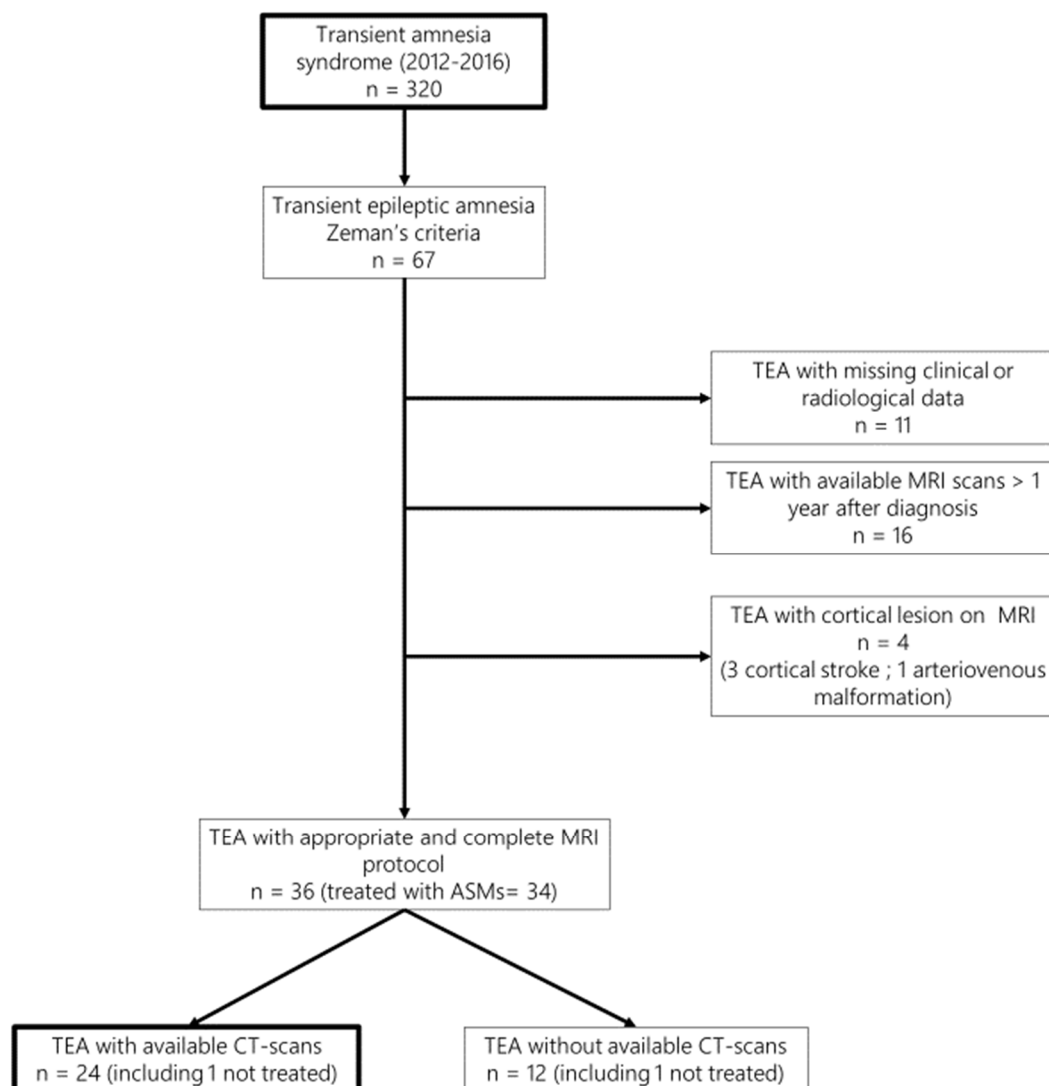
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## Figures

**Figure 1: Study flow-chart**

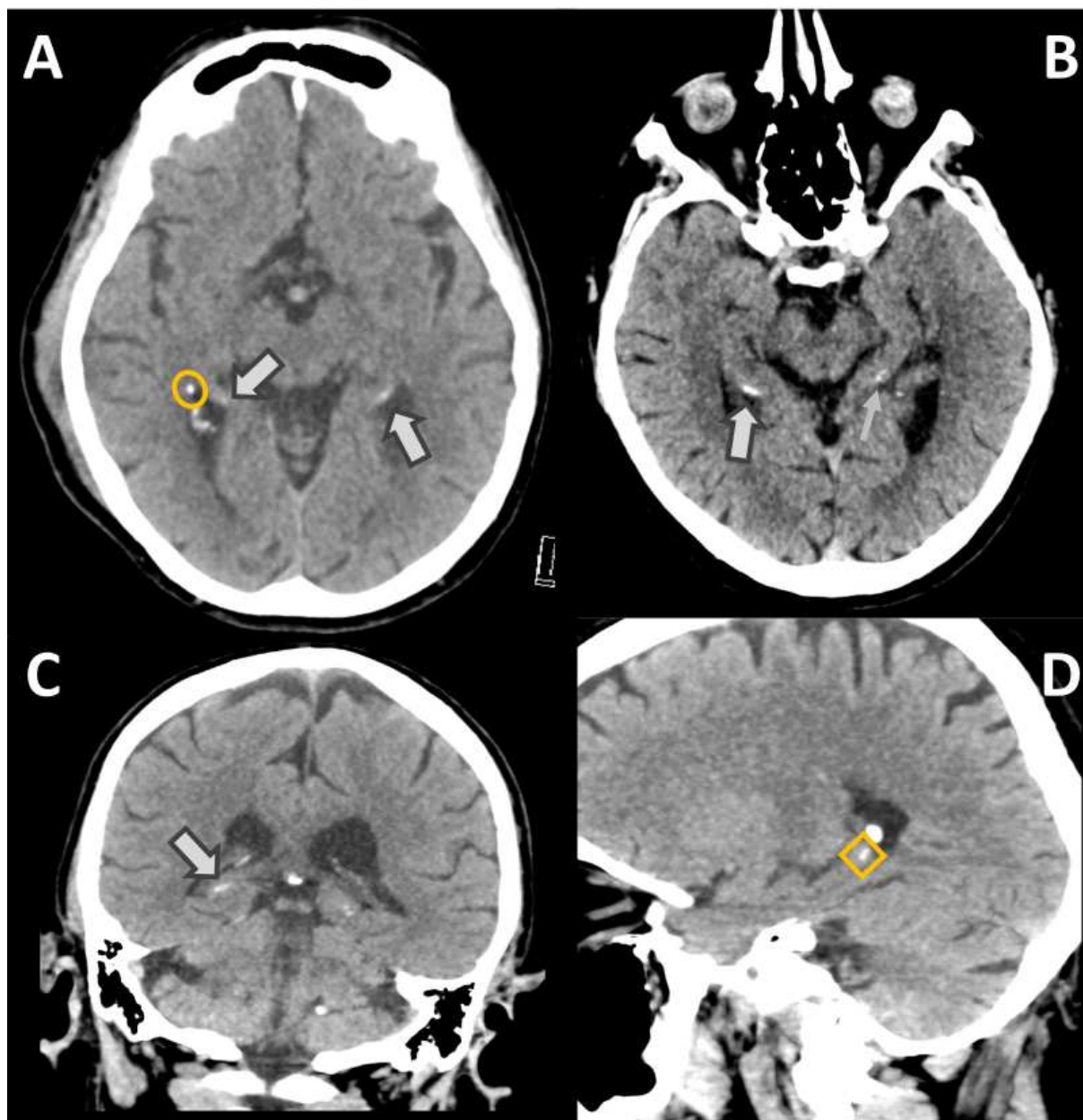




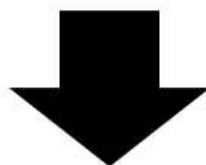
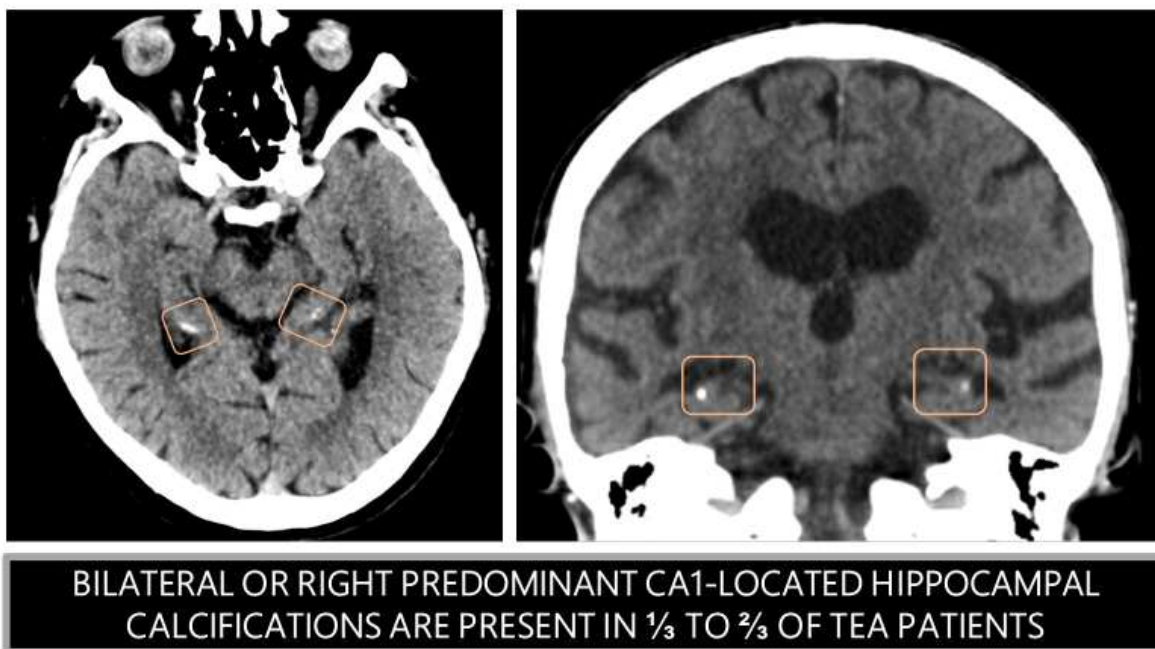
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Note: 2A: patient #4, bilateral subtle HCs (thick arrows), not to be confused with choroidal calcifications (orange circle); 2B, C: bilateral HCs of patient #9 (arrows), predominating on the right side (thick arrows); 2D: right HCs of patient #9, located in the CA1 region of the tail of the hippocampus (orange square).



CA1 disruption potentially explains the clinical features of TEA:

- ⇒ Interictal memory complaints  $\pm$  objective deficits on tests
- ⇒ Iterative short paroxysmal amnesias resembling TGA
- ⇒ Persistent memory complaints despite seizure cessation