Epilepsy & Behavior 79 (2018) 93–99

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Pre- and long-term postoperative courses of hippocampus-associated memory impairment in epilepsy patients with antibody-associated limbic encephalitis and selective amygdalohippocampectomy

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ARTICLE INFO

Article history:
Received 11 August 2017
Revised 25 October 2017
Accepted 26 October 2017
Available online 16 December 2017

Keywords:
Limbic encephalitis
Amygdala
Hippocampus
Selective amygdalohippocampectomy
Memory

ABSTRACT

Objective: Limbic encephalitis (LE) is defined by mesiotemporal lobe structure abnormalities, seizures, memory, and psychiatric disturbances. This study aimed to identify the long-term clinical and neuropsychological outcome of selective amygdalohippocampectomy (sAH) in drug-resistant patients with temporal lobe epilepsy due to known or later diagnosed subacute LE not responding to immunotherapy associated with neuronal autoantibodies.
Methods: In seven patients with temporal lobe epilepsy due to antibody positive LE (glutamic acid decarboxylase (GAD65): n = 5; voltage-gated potassium channel complex (VGKC), *N*-methyl D-aspartate receptor (NMDAR): n = 1; Ma-2/Ta: n = 1) sAH (6 left, 1 right) was performed. Those patients underwent repeated electroencephalography (EEG) recordings, magnetic resonance imaging (MRI) volumetry of the amygdala and hippocampus, and neuropsychological examinations and were followed up for 6–7 years on average.
Results: Verbal memory and figural memory were affected in 57% of patients at baseline and 71% at the last follow-up. At the last follow-up, 14% of the patients had declined in verbal memory and figural memory. We observed improved memory in 43% of patients regarding figural memory, but not in a single patient regarding verbal memory. Repeated evaluations across the individual courses reveal cognitive and MRI dynamics that appear to be unrelated to surgery and drug treatment. Three of the seven patients with LE with different antibodies (NMDAR: n = 1, Ma-2/Ta: n = 1 and GAD65: n = 1) achieved persistent seizure freedom along with no accelerated memory decline after surgery. Two of the five GAD65-antibody patients positive with LE showed progressive memory decline and a long-term tendency to contralateral hippocampus atrophy.
Conclusions: While memory demonstrated some decline in the long run, what is most important is that a progressive decline in memory is seldom found after sAH in patients with LE. Moreover, the dynamics in performance and MRI before and after surgery reveal disease dynamics independent of surgery. Selective amygdalohippocampectomy can lead to seizure freedom, but should be considered as a last resort treatment option for drug-resistant patients with temporal lobe epilepsy due to LE. Particular caution is recommended in patients with GAD65-LE.

1. Introduction

Declarative memory formation relies on the hippocampus [1]. Hippocampal lesions cause memory loss [2]. Selective amygdalohippocampectomy (sAH) is a standard surgery technique to treat drug-resistant temporal lobe epilepsy (TLE) leading to seizure freedom in 51–83% of patients [3–9], and although this type of surgery is selective and safe, figural or verbal memory decline is observed in 27–50% at a standard interval of one year after temporal lobe surgery [10,11]. While this can be considered as a possible cognitive risk associated with temporal lobe surgery, a question of major importance is what the cognitive outcomes are if the patient undergoes surgery while suffering from an underlying disease, as is the case with limbic encephalitis (LE), which is an autoimmune disorder accompanied by signal alterations in temporal lobe structures, seizures, memory, and affective disturbances associated with neuronal autoantibodies [12]. Severe memory disturbances such as impaired verbal and figural memory, accelerated long-term forgetting and the loss of autobiographical memory can be induced by LE associated with autoantibodies against intracellular localized enzyme glutamic acid decarboxylase (GAD65) [13,14]. Individual case reports and case series highlight sAH as a useful additional

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https://doi.org/10.1016/j.yebeh.2017.10.033
1525-5050/

treatment option in drug-resistant patients with epilepsy with LE associated with LGI1 autoantibodies [15], no proven antibodies [16], or different neuronal antibodies (GAD65-, Ma2-, Hu-, LGI1-, and contactin-associated protein 2 receptor (CASPR2) antibodies) [17]. However, so far no study has investigated the long-term memory outcome after sAH in patients with LE. Thus, we explored in this study whether sAH affects figural and verbal memory performance in the long run in patients with LE and helps them attain continuing seizure freedom.

2. Methods

This retrospective study was performed in 7 patients (4 females, 35.3 ± 10.2 years). Their inclusion criteria consisted of an age ≥ 18 years, an LE diagnosis with proven autoantibodies in the peripheral blood (PB) or cerebrospinal fluid (CSF), and an sAH in the past. The reader should be aware that in four of the seven operated patients, LE associated with Ma-2/Ta in one patient and GAD65-antibodies in three patients was diagnosed after surgery and that those patients underwent surgery unaware that they were suffering from LE. The remaining three patients had subacute LE that had failed to respond to treatment (methylprednisolone, mycofenolatmofetil, cyclophosphamide, immunoadsorption), and the decision for surgery was made because the seizures were obviously unilateral and persisting. The LE diagnosis was made if (1) patients exhibited a subacute onset of memory deficits, temporal lobe seizures, and/or psychiatric symptoms, (2) uni- or bilateral brain abnormalities in T2-weighted images (T2)/fluid-attenuated inversion recovery (FLAIR)-weighted images in magnetic resonance imaging (MRI), and (3) CSF pleocytosis or electroencephalography (EEG) abnormalities (epileptic potentials or focal slowing in the temporal region) [18]. If the currently accepted criteria of Graus [12] for definitive and possible autoimmune encephalitis are applied, 6 patients in our study at different time points (T1–T4) fulfilled those criteria retrospectively for definitive autoimmune encephalitis including the criterion of bilateral brain abnormalities in T2/FLAIR-weighted images in MRI. To detect brain abnormalities in MRI, we used the combination of (1) MRI volumetry of the hippocampus and amygdala contralateral to the resected side and (2) radiologic MRI evaluation (for details see neuroimaging in methods). Following the new classification criteria, one female patient must be classified as possibly having autoimmune encephalitis. However, apart from unilateral MRI brain abnormalities in the temporal lobe, she fulfills all other criteria of LE's clinical presentation. Moreover, the later histological analysis of this patient's resected brain specimen confirmed her suspected LE. The autoantibodies in PB and the CSF were usually determined via indirect immunohistochemistry, seldom by radioimmunoprecipitation assay [EUROIMMUN; neuropathology laboratory (AJB, Bonn)]. We investigated in all our patients a variety of autoantibodies already described in detail [14]; GAD65-antibodies had been detected in the PB in 5/7 patients, whereas 3/5 patients presented GAD65-antibodies also in the CSF. Furthermore, we detected voltage-gated potassium channel complex (VGKC)- and *N*-methyl D-aspartate receptor (NMDAR)-antibodies in one patient's PB, and Ma-2/Ta-antibodies in another patient's PB and CSF. Our study patients were selected from those diagnosed with sAH, LE, and TLE documented in our database between 1998 and 2016. All had undergone neuropsychological, EEG, and MRI investigations. In addition, 19 healthy subjects (14 females) aged a mean 33 ± 10.4 years (who did not differ in age from the patients) underwent MRI. Our study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee at the Medical Faculty of the University of Bonn.

2.1. Neuropsychology

Verbal and figural memory functions were assessed at individual time points in all patients. Baseline was defined as T1 and the last study follow-up as T4. A year before surgery was defined as T2, and two years after surgery as T3. We applied the "Verbaler Lern und Merkfähigkeitstest" (VLMT) to assess verbal memory capacity as previously described [19]. To measure figural and visual–spatial learning and memory functions, we employed the revised "Diagnosticum für Cerebralschädigung" (DCS-R) as described previously in detail [20]. We employed a compound verbal and figural memory score calculated according to the summary scores of standardized memory subfunctions (m = 100 ± 10) [verbal memory: learning = immediate recall, memory = free recall after distraction and delay, and recognition; figural memory: learning = immediate recall (reconstruction) and delayed recognition] divided by the number of variables. We rated a significant impairment with scores ranging below mean – 1 standard deviation (SD) (values <90) and improvement or deterioration whenever a patient demonstrated a change in performance of more than one standard deviation (>/< 10) in the positive (improvement) or negative (deterioration) direction.

Table 1
Demographics and clinical characteristics of patients.

Parameter	Mean and SD
Age (y)	35.3 ± 10.2
Gender	5 f. 2 m
Follow-up (y)	6.5 ± 4.3
Age at surgery (y)	30 ± 11.6
Education	4/7 patients: higher education, 3/7 patients: basic education
Comorbidities	3× DM, 1× depression, 1× adipositas
Histology	2/7 patients Wyler III/IV, neuronal loss in 4/7 patients in hippocampal subfields, t-cell infiltrates in 3/7 patients
CSF cell count/5 μl	7 ± 13
CSF protein mg/l	435.7 ± 73
CSF oligoclonal bands	4/7 patients
CSF BBB disturbance	1/7 patients
Seizure onset (y)	21.4 ± 12.4
Seizure freedom (y)	3/7 patients (0.75, 3.1, 3.3)
Focal seizures T1–T4 (per month)	24.1 ± 21.1, 18.9 ± 12.6, 7 ± 4.6, 12.9 ± 12.9
Complex focal seizures T1–T4 (per month)	18.1 ± 10.2, 20.1 ± 10.6, 65 ± 44.4, 51.8 ± 42.2
Secondarily generalized seizures T1–T4 (per month)	2.3 ± 2.27, 1.8 ± 1.7, 4.9 ± 1.85, 0 ± 0
Engel's class I T3; T4 in %	2/7 patients (29%), 3/7 patients (43%)
Engel's class II T3; T4 in %	1/7 patients (14%), 3/7 patients (43%)
Engel's class III T3; T4 in %	1/7 patients (14%), 0/7 patients (0%)
Engel's class IV T3; T4 in %	3/7 patients (43%), 1/7 patients (14%)
EEG score T1 (0–6)	5.3 ± 0.47
EEG score T2 (0–6)	3.3 ± 1.6
EEG score T3 (0–6)	4.7 ± 1.2
EEG score T4 (0–6)	3.5 ± 1.6
Immunotherapeutic agent/cumulative dose	5× MP (42 ± 33 g), 3× AZA (19.6 ± 10.6 g), 3× P (6.5 ± 4.5 g), 2× MM (36 ± 2 g), 2× CS (21 ± 11 g), 2× IA (12 ± 11×), 1× DM (144 mg), 1× PP, 1× IVIG
First immunotherapy (month after diagnosis, agent)	Immediately: 5/7 patients MP, 1/7 AZA, 1/7 patients intravenous IVIG
Second immunotherapy (month after diagnosis, agent)	7 ± 4 months: 4/7 patients (IA, PP, DM, or CP)
Third immunotherapy (month after diagnosis, agent)	8 ± 4 months: 3/7 patients (CP, P)
AED (T1)	1.4 ± 0.98
AED (T2)	1.7 ± 0.49
AED (T3)	1.9 ± 0.7
AED (T4)	2 ± 1.3

Abbreviations: Abs = antibodies, AED = antiepileptic drugs, AZA = azathioprine, BBB = Blood–brain barrier, CSF = cerebrospinal fluid, CS = cyclophosphamide, DM = dexamethasone, DM = diabetes mellitus, EEG = electroencephalography, f = female, m = male, IA = immunadsorption, IVIG = intravenous immunoglobulines, MM = mycophenolatmofetile, MP = methlyprednisoline, PB = peripheral blood, PP = plasmapheresis, sAH = selective amygdalohippocampectomy, SD = standard deviation, T1 = baseline, T2 = one year before surgery, T3 = 1–2 years after surgery, T4 = last follow-up, y = years.

2.2. Neuroimaging

Brain MRI was done utilizing a 3 Tesla MRI scanner at the Life & Brain Institute (Magnetom Trio, Siemens, Germany); MRI volumetry of the hippocampus and amygdala was performed via the FreeSurfer image analysis suite (Freesurfer stable Version 6, Martinos Center, Boston, USA) in patients and controls [21–23]. Radiologic criteria reconcilable with LE are denoted by swollen or atrophied and hyperintense mesiotemporal structures on FLAIR images and T2-weighted images.

2.3. Immunotherapy and antiepileptic drugs

Intravenous methylprednisolone (1000 mg/d, 3 to 5 days) was applied monthly over four to six months in five patients, and three GAD65-antibodies-positive patients were given oral prednisolone (80–100 mg/d). Further immunotherapeutic agents such as cyclophosphamide, intravenous immunoglobulins, dexamethasone, plasmapheresis, or immunoadsorption were administered in some patients according to standard therapeutic regimens (Table 1). Antiepileptic drugs (AED) were prescribed to enable patients to achieve seizure control.

2.4. Electroencephalography

All patients underwent a 24-hour EEG recording (10–20 system according to international EEG convention) at each time point (T1 to T4). An EEG score (1–6) reported in detail previously [14] was used to grade EEG abnormalities.

2.5. Seizure classification

The postoperative seizure outcome was defined according to the Engel classification (Class 1: free of seizures, Class 2: rare disabling seizures, Class 3: worthwhile improvement, Class 4: not worthwhile improvement) [24]. Seizure frequency was identified in line with patients' and their relatives' reports.

2.6. Statistics

Statistical analysis was performed utilizing SPSS (V.23.0, IBM, Armonk, New York, USA) and Sigma Statistics (Version 11, 2008, San Jose, California, USA). Graphic illustrations were made via Sigma Plot (Version 11, 2008, San Jose, California, USA). If not stated otherwise, the data are expressed as mean and standard error of the mean. Normal distribution of the data was checked by the Shapiro–Wilk test. Data with normal distribution were analyzed by the student's *t*-test, whereas not normally distributed data were subjected to the Mann–Whitney *U* test. Absolute volumes in mm^3 of the amygdala and hippocampus were used to calculate the z-score based on the mean and standard deviation of control values according to the formula: z = single value of patients-mean of controls/standard deviation of controls. Augmentation of each structure was defined as a z-score value's increase of ≥1, and an atrophy of each structure was specified when the z-score value is ≤1.

3. Results

We identified seven patients with autoantibody-associated LE and sAH (demographic and clinical characteristics of patients see Tables 1 and 2). Overall, LE was diagnosed 8.9 ± 4.2 years after symptoms' onset, and surgery took place 8.6 ± 3.2 years after symptoms' onset. In 3/7 patients, LE was diagnosed 4.6 ± 2.3 years before, and in 4/7 patients 4.1 ± 5.1 years after surgery. In the latter patients, the LE diagnosis was delayed after sAH due to the late detection of autoantibodies in testing samples. Histological analysis confirmed the LE diagnosis retrospectively in all patients (Table 1). The number of AED did not differ over time (T1 vs. T4, *t*-test: p = 0.44) and one year before (T2) and 1.6 ± 1.1 years after (T3) surgery (T2 vs. T3, Mann–Whitney *U* test: p = 0.81). The immunotherapy applied differed among patients and time points (Table 1, Fig. 1A).

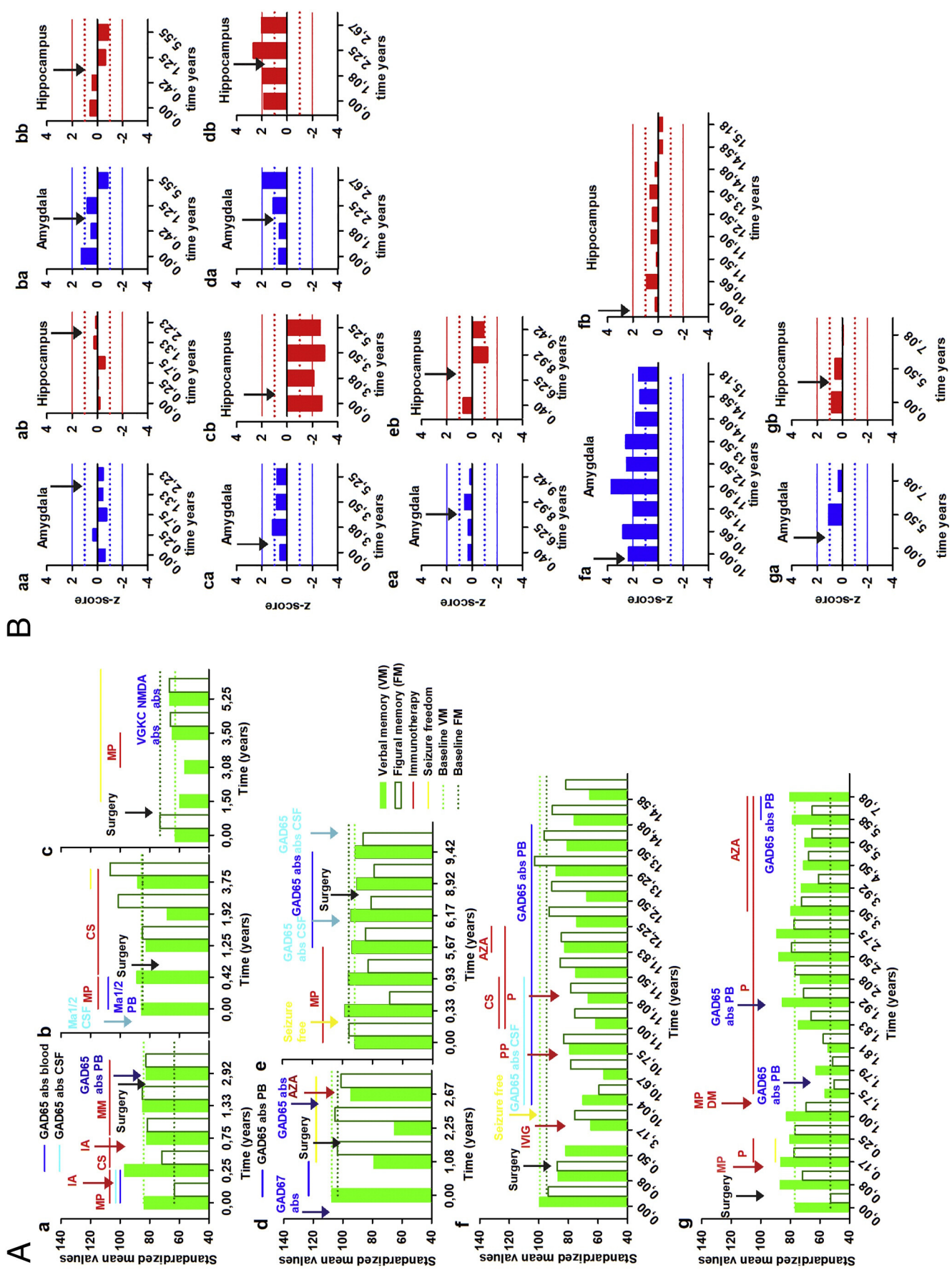
3.1. Long-term outcome in verbal memory

The individual dynamics in individual patients' verbal memory scores throughout the study period are shown in Fig. 1A (see also Table 2). At T1, verbal memory impairment was present in 4/7 patients (57%). The number of patients with verbal memory impairment increased to 6/7 patients (86%) at T2 (Fig. 2; Tables 2, 3). Patients impaired at T2 remained impaired in verbal memory at T3 after surgery, and none of the unimpaired patients worsened (Figs. 1A, 2, Table 2). On the group level, we noted a nonsignificant trend toward deteriorated standardized verbal memory values between T2 and T3 (*t*-test, p = 0.56; Figs. 1A, 2). After 6.5 ± 1.5 years (T4), verbal memory was affected in 5/7 (71%) patients (Fig. 2, Table 3). The standardized verbal memory scores did not significantly change between baseline (T1) and the final follow-up (T4) (*t*-test: p = 0.45, Figs. 1A, 2). Individually, no patient improved

Table 2
Individual patient characteristics.

Patient	a	b	c	d	e	f	g
MRI T1	L Hipp, Amy↑	L Hipp, Amy↓ R Amy↑	L Hipp↓, Amy↑ R Hipp↓	L Hipp↑ L Amy↑	L/R Hipp↓	L Hipp ↓	R Hipp ↓
MRT T2	L Hipp, Amy↑	L Hipp, Amy↓	R/L Hipp↓	L Hipp↑		L Hipp ↓	R Hipp ↓
MRT T3	L sAH	L sAH	L sAH R Amy↑, Hipp↓	L sAH R Amy↑, Hipp↑	L sAH R Hipp↓	L sAH	R sAH L Amy↑
MRT T4	L sAH	L sAH	LsAH R Hipp↓	L sAH R Amy↓, Hipp↑	L sAH R Amy↓, Hipp↑	L sAH R Amy↓	R sAH L Hipp, Amy↑
LE diagnosis	Before surgery	Before surgery	After surgery	After surgery	Before surgery	After surgery	After surgery
Antibodies	GAD65 PB GAD65CSF	Ma-2/Ta PB Ma-2/Ta CSF	NMDAR PB VGKC PB	GAD65 PB	GAD65 PB GAD65 CSF	GAD65 PB GAD65 CSF	GAD65 PB
Surgery access	Pterional	ant temp	transsylvic	transsylvic	transsylvic	transsylvic	transsylvic
Follow-up (y)	2.92	3.75	5.25	2.67	9.42	14.58	7.08
Seizure free	No	Yes	Yes	Yes	Intermittent	Intermittent	Intermittent
Verbal memory T1	Impaired	Impaired	Very severely impaired	Nonimpaired	Nonimpaired	Nonimpaired	Severely impaired
Verbal memory T4	Impaired	Impaired	Very severely impaired	Nonimpaired	Nonimpaired	Very severely impaired	Impaired
Figural memory T1	Impaired	Impaired	Very severely impaired	Nonimpaired	Nonimpaired	Nonimpaired	Very severely impaired
Figural memory T4	Impaired	Nonimpaired	Very severely impaired	Nonimpaired	Impaired	Impaired	Very severely impaired

Abbreviations: Ant temp = anterior temporal, CSF = cerebrospinal fluid, impaired = ≥1 SD above the mean; L = left, PB = peripheral blood, MRI = magnetic resonance imaging, R = right, sAH = selective amygdalohippocampectomy, severely impaired = ≥2 SD above the mean; very severely impaired = ≥3 SD above the mean, T1 = baseline, T2 = one year before surgery, T3 = 1–2 years after surgery, T4 = last follow-up, y = years. MRI features at different time points (T1–T4) are based on the MRI volumetry and radiologic evaluation of MRIs (see methods).


A
B
Standardized mean values
Time (years)
GAD65 abs blood
GAD65 abs CSF
GAD65 abs PB
IA
CS
MM
MP
Surgery
Ma1/2 CSF
Ma1/2 PB
VGKC NMDA abs
GAD67 abs
AZA
Seizure free
GAD65 abs CSF
PP
IVIG
P
DM
Verbal memory (VM)
Figural memory (FM)
Immunotherapy
Seizure freedom
Baseline VM
Baseline FM
Amygdala
Hippocampus
z-score
time years

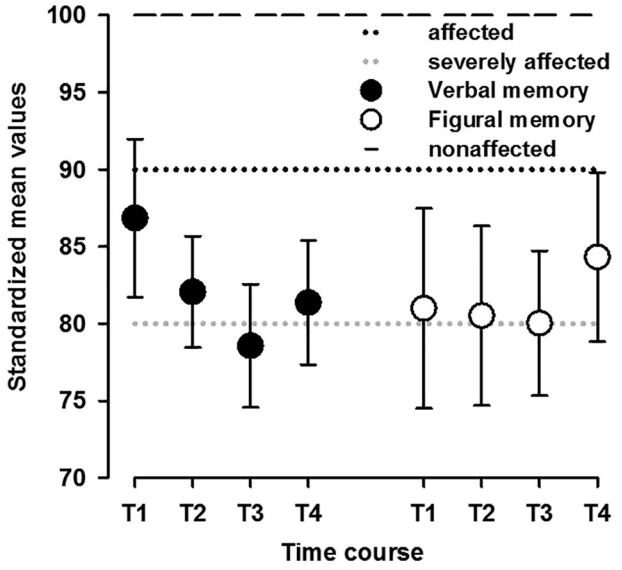


Fig. 2. Standardized mean values of figural and verbal memory functions from 7 patients at baseline (T1), one year before surgery (T2), two years after surgery (T3) and at last follow-up (T4).

and one patient (GAD65-antibodies, patient f) deteriorated (i.e., >3 SD below the mean) in verbal memory scores (14%) (Table 3).

Looking at patient subgroups, 2/5 (40%) of patients with LE with GAD65-antibodies (GAD-LE) showed impaired verbal memory at baseline (T1) and were still impaired at the last follow-up (T4), 1/5 patients (20%) of the patients with GAD-LE exhibited a deterioration at T4 (8 years after sAH). Verbal memory in NMDAR- and Ma-2/Ta-antibodies-positive patients was impaired at baseline (T1), with no alterations at follow-up (T4; 4–5 years after sAH) (Fig. 1A). Verbal memory improved in 2/7 patients at follow-up (T4) along with the application of cyclophosphamide in patient b (Ma-2/Ta-antibodies) and methylprednisolone in patient c (VGKC-, NMDAR-antibodies).

3.2. Long-term outcome in figural memory

Fig. 1A (Table 2) depicts the dynamics in individual patients' figural memory scores within the observation periods. Four of the seven patients (57%) exhibited impaired figural memory at baseline (T1) (Fig. 2, Table 3) and 5/6 patients (83%) were impaired in figural memory scores at T2 and after surgery at T3 (Figs. 1A, 2, Table 3). After 6.2 ± 1.6 years at T4, 5/7 patients (71%) presented an impaired figural memory (Fig. 2, Table 3). On the group level, figural memory scores did not change between T1 and T4 (*t*-test, p = 0.72; Figs. 1A, 2; Table 2). However, three patients (GAD65-, Ma2-/Ta antibodies; Fig. 1A a, b, g) (43%) improved, whereas one patient's figural memory function (GAD65-antibodies, Fig. 1A f) deteriorated (Fig. 1A, Table 3).

In addition, we observed no decline in verbal memory scores at T4 compared to T1 in the seizure-free patients after sAH over the long run.

The individual analysis of figural memory scores in two seizure-free patients with NMDAR-and VGKC-antibodies in one patient (Fig. 1A b) and GAD-65 antibodies in another patient (Fig. 1A d) did not reveal deteriorated figural memory scores in the long term at T4 compared to T1. Our subgroup analysis showed that in 2/5 (40%) of patients with GAD-LE, figural memory was impaired at T1 and with deterioration in 2/5 (40%) of patients with GAD-LE in figural memory after about 8.3 years. The severely impaired figural memory of one patient with NMDAR-antibodies at T1 deteriorated after 5.3 years (Fig. 1A c), while another patient's figural memory (Fig. 1A b: Ma-2/Ta-antibodies) was impaired at T1, but recovered after approximately 3.8 years (T4). Figural memory improved in 3/7 patients after immunotherapy via cyclophosphamide in two patients (Fig. 1A a, b: GAD65-, Ma-2/Ta-antibodies), immunoadsorption in one patient, and methylprednisolone in another patient (Fig. 1A e, GAD65-antibodies).

Table 3
Verbal and figural memory impairment in limbic encephalitis patients.

Functional memory domain	T1	T2	T3	T4
Verbal memory				
Affected	57%	86%	86%	71%
Improved ↑/Deteriorated ↓ (≥1 SD)	0%/29%↓ (T1 vs. T2), 14%↑/14%↓ (T2 vs. T3), 14%↑/ 14%↓ (T3 vs. T4), 0% /14%↓ (T1 vs. T4)			
Figural memory				
Affected	57%	83%	83%	71%
Improved ↑/Deteriorated ↓(≥1 SD)	14%↑/14%↓ (T1 vs. T2), 17%↑/17% ↓(T2 vs. T3), 0%↑/0% ↓(T3 vs. T4), 43%↑/14%↓ (T1 vs. T4)			

Abbreviations: SD = standard deviation, T1 = baseline, T2 = one year before surgery, T3 = 1–2 years after surgery, T4 = last follow-up.

3.3. Neuroimaging of the amygdala

Magnetic resonance imaging features of the amygdala in individual patients at T1–T4 are depicted in Table 2. Amygdala enlargement is a sign of potential LE reactivation [25,26]. We detected higher amygdalar volume (i.e., >1 SD above the mean) in the unresected amygdala after surgery compared to controls in 5/7 patients at different time points during the study (Fig. 1B ba: 0 years, Fig. 1B ca: 3.1 years, Fig. 1B da: 2.3 and 2.7 years, Fig. 1B fa: 11.5, 14.1–15.2 years and Fig. 1B ga: 5.5 years after baseline). Furthermore, we observed much greater amygdalar volume in 1/7 patients after sAH (Fig. 1B fa: 10–10.7 and 11.9–13.5 years after baseline) (i.e., >2 SD above the mean) than in the controls.

3.4. Neuroimaging of the hippocampus

Table 2 demonstrates MRI abnormalities in the hippocampus in individual patients at T1–T4. In two patients with GAD65-antibodies (Fig. 1A e, f; B eb, B fb) and one patient with Ma1/2 antibodies (Fig. 1A b, B bb), we detected the tendency to lose hippocampal volume. The hippocampus of one patient with GAD65-antibodies is atrophic below the controls' mean (i.e., <2 SD below the mean) at 8.9 years after baseline (Fig. 1B eb). In one patient with NMDAR- and VGKC-antibodies, hippocampal volume was smaller compared to controls (i.e., <2 SD below the mean) 3.1–5.2 years after baseline (Fig. 1B cb).

Hippocampal volume was enlarged in 1/7 patients with GAD65-antibodies compared to controls after baseline and surgery (i.e., >1 SD above the mean) (Fig. 1B db: at 1.1 and 2.6 years after baseline). The volume of patient d's hippocampus at 2.3 years after baseline was very enlarged compared to controls (i.e., >2 SD above the mean).

Fig. 1. (A) Time course of figural and verbal memory impairment in patients with limbic encephalitis associated with neuronal antibodies. Standardized mean values are indicated on the ordinate. The antibodies detected in the peripheral blood (PB) are indicated in blue lines or arrows. Bright blue lines or arrows indicate antibodies in the cerebrospinal fluid (CSF). Abs = antibodies, AZA = azathioprine, CS = cyclophosphamide, GAD65 = glutamic acid decarboxylase 65, IA = immunoadsorption, IVIG = immunoglobulins, MM = mycofenolatmofetil, MP = methylprednisolone, NMDAR = *N*-methyl D-aspartate receptor, P = prednisolone, PP = plasmapheresis. Time point of surgery is indicated by a black arrow. **(B)** Z-scores of the amygdala in (aa–ga) and hippocampus (ab–gb) calculated from absolute amygdalar and hippocampal volumes of each patient are depicted over individual time points in years. The upper and lower borders of the one-fold standard deviation of controls is shown by dotted blue (amygdala) and dotted red lines (hippocampus). In addition, the upper and lower borders of the twofold standard deviation are depicted by blue lines (amygdala) and red lines (hippocampus). Time point of surgery is indicated by a black arrow.

3.5. Seizures and EEG

Interictal-EEG scores did not change significantly over time (Mann–Whitney *U* test, $p = 0.09$) or before and after surgery (*t*-test, $p = 0.17$, Table 1). The frequency of focal, complex focal, and secondarily generalized seizures was not altered after surgery and at last follow-up compared to baseline (*t*-test, $p \geq 0.34$, Table 1). Surgery led to seizure freedom in one patient for approximately one year (Fig. 1A b, Ma-2/Ta-antibodies) and in two patients (Fig. 1A c, VGKC- and NMDAR-antibodies; Fig. 1A d, GAD65-antibodies) for about three years. A year after surgery, 29% were in Engel class I, 14% in Engel class II or III, and 43% in Engel class IV, whereas 43% attained Engel class I at the last study follow-up, 43% Engel class II, 0% in Engel class III, and 14% Engel class IV (Table 1). There were no significant differences in Engel classes I–IV between baseline and last follow-up after sAH and immunotherapeutic treatment (Mann–Whitney *U* test, $p > 0.21$).

4. Discussion

Our main findings show that 57% of patients were impaired in either verbal or figural memory at baseline. Memory impairment is frequently diagnosed in patients with TLE with LE associated with Ma-2/Ta-, NMDAR-, VGKC-, and GAD65-antibodies [14,27–30]. Taking baseline impairments into consideration, the major finding of this study is that despite epilepsy surgery, verbal memory and figural memory deteriorated in only 14% of the patients with LE who were followed up for an average of 6–7 years (min. 2.7 years, max. 14.6 years). In contrast: 43% demonstrated an improvement in memory, but only in figural, not verbal memory. While this describes the change between two measurement points (baseline and last follow-up), we noted considerable variation in memory performance in the time between.

Following the dynamics on an individual level, memory tended to deteriorate during the time before surgery. The time after sAH was characterized by transient improvements and deteriorations. In part, as in one patient with LE with VGKC- and NMDAR-antibodies, the memory decline was outside the range of measurement because he had already exhibited a very severely affected memory at baseline. The changes we observed after surgery are no different from what one would expect after TLE surgery in general [7,10,11]. Looking at the individual memory courses over our entire observation periods, it should be noted that the variations in memory performance over time indicate a functional dynamic independent of surgery. Although most patients underwent diverse immune treatments in between, effects of immune treatment on memory were hard to discern. The same is true for seizure control. Selecting and viewing any two subsequent assessments without the context of the preceding and following evaluations could easily lead to misinterpretations about the disease course or effects of interventions. This is surely a new finding of major interest for future evaluations of this group of patients.

Comparing the memory outcomes of surgically-treated versus purely pharmacologically-treated patients with GAD-LE from our previous report [14,27], the present study provides evidence of worse figural (−40%) and verbal memory performance (−20%) after immunotherapy plus sAH than with immune treatment alone. However, this investigation's observation period was longer. Comparing this study's short and long-term memory outcomes in patients with LE with outcomes observed in TLE in general, the short and long-term verbal and figural memory decline our patients with LE exhibited in is in line with previous reports of memory decline after left temporal lobe surgery [7,11,31,32]. Interestingly, the long-term figural memory outcome is worse in patients with TLE who did not undergo surgery over a long 13-year period [33], supporting the hypothesis that surgery in patients with LE does not trigger the progression of autoimmunity.

One reason why the memory decline did not accelerate in most of our patients is that a functional reorganization of the memory network may have occurred [34,35]. In particular, memory functions might have been compensated due to an early disease onset, or as a function of time after sAH. Moreover, one can also argue that episodic memory is not just based on the hippocampus. The entorhinal cortex, for example, is often unaffected by sAH; it is an independent structure to reactivate episodic memory [36]. One factor associated with improved memory is higher education [31]. We noted the protective factor of higher education in 4/7 of our patients, and 3/4 of them revealed no relevant memory decline over the long-term. Other predictors of stable memory performance [35,37,38] that our patients fulfill are young age (6/7 patients ≤39 years) and good memory performance prior to surgery (3/7 patients), and seizure freedom in 3/7 (43%) patients associated with NMDAR-, VGKC-, GAD65-, or Ma-2/Ta-antibodies.

Of the patients with LE, 43% achieved seizure freedom (Engel class I) at the last study follow-up after sAH (T4). This is below the reported seizure freedom associated with TLE surgery three years after surgery [39]. One reason for poorer seizure outcome might be the more bilateral manifestation of epilepsy compared to the usual candidate for epilepsy surgery who presents with unilateral pathology and epilepsy.

Bilateral manifestation is a prerequisite for diagnosing definitive autoimmune encephalitis according to the Graus criteria [12]. We detected bilateral manifestations of LE in MRI in three patients at study onset, in six patients during the study period, and in five patients after sAH during the study. This indicates progression and spread of the disease on a structural level. The bilateral manifestation after sAH could be a sign of LE reactivation by spreading to the nonpathological side, or reinflammation of a side affected earlier during the LE time course. Together with persisting or newly occurring seizures and memory disturbances (as in the three individuals with GAD65-antibodies (patients e, f, g) and one with NMDAR- and VGKC-antibodies (patient c)), the bilateral manifestation could be assumed to be caused by relapsing LE. What remains unclear is whether sAH has an active impact on these fluctuations, or whether LE reactivation would have occurred either way due to unknown causes. However, the bilateral manifestation might partly also explain the dynamic fluctuations in long-term memory outcome that seem to be independent of sAH.

4.1. Limitations

An important limitation study is its retrospective and uncontrolled observational design. The evaluated group of patients was small and heterogeneous in terms of the antibodies. Subgroup analyses were not possible, and changes had to be described mainly on the individual level. Another problem that needs to be considered is that some patients had undergone surgery not knowing that they were suffering from LE, and that this decision was made for others deliberately knowing that those patients were suffering from LE. Furthermore, no consistent immunological treatment took place. Which type of intervention was chosen and when treatment was escalated or discontinued was decided individually. We nevertheless feel that these longitudinal data are well-suited to shed particular light on LE's disease dynamics and the relative effects of any treatment (surgical, immunological, antiepileptic) when assessments and evaluations are restricted to one or two time points only.

In conclusion and in consideration of our investigation's limitations, its major finding is that surgery seldom led to progressive memory decline in this group of operated patients over the long run. Another finding of importance is that in LE there are dynamics on a functional and structural level that appear to be partly treatment-independent. Functional and structural changes in some patients provide evidence that LE can have an intrinsic and probably surgery-independent tendency to progress over time. Accordingly, considering the risk of LE progression, any patient with LE being considered for surgery must undergo thorough examination. Especially the patients with GAD-LE with a relapsing–remitting disease course who did not achieve seizure freedom after sAH raise concerns about the indication for surgery in this type of LE.

5. Conclusions

The longitudinal outcome of material-specific memory impairment over approximately six years in patients with LE presenting antibodies against GAD65, NMDAR, VGKC, and Ma-2/Ta who have undergone sAH is similar to that in seen in the general patient with TLE who underwent sAH. Selective amygdalohippocampectomy has no impact on the dynamic course of long-term figural and verbal memory in LE that declines slowly over years. Seizure control was poor in our patients, but this may be due to the high proportion of seizure reoccurrence in our patients with GAD-LE after sAH. However, seizure freedom after sAH seems to be a factor associated with no accelerated figural and verbal memory decline and could be interpreted as a full remission of LE.

Taken together, sAH can be a valuable therapeutic option in drug-resistant TLE due to LE associated with neuronal antibodies, and within our operated patient group's age range, there was in particular no evidence of progressive memory decline into an amnestic syndrome due to damage to the contralateral nonresected hippocampi. This therapeutic option needs to be carefully assessed in patients with GAD-LE, as it is they who often suffer memory decline and seizure reoccurrence over the long run.

Disclosure of conflict of interests

CH has received honoraria, travel support, license fees, and research funding from Desitin, EISAI, UCB Pharma, GW-Pharmaceuticals, and EU grants EAHC Epilepsy & ERN Epicare. CEE has served as a paid consultant for UCB Pharma, Desitin, and Pfizer. The remaining authors (AJB, GW, LE, NH, TR) have no conflicts of interest.

Funding

LE received support from the Promotionsstipendium der Uni Bonn/EKFS (BonnNi) and the “Else-Kröner-Fresenius Stiftung”.

Ethical publication statement

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.

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