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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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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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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.