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Cognitive features and surgical outcome of patients with long-term epilepsy-associated tumors (LEATs) within the temporal lobe

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ABSTRACT

Objective: The objective of the study was to evaluate cognitive and epilepsy-related features in 166 surgically treated patients with epilepsy with long-term epilepsy-associated tumors (LEATs) located in the temporal lobe.
Method: Pre- and postsurgical cognitive as well as the one-year seizure outcome of adult patients with histopathologically confirmed LEATs (28 grade-I dysembryoplastic neuroepithelial tumors (DNET), 95 grade-I gangliogliomas (GG), 24 grade-I pilocytic astrocytomas (PA), 9 grade-II pleomorphic xanthoastrocytoma (PXA), 10 grade-II diffuse astrocytoma (DA)) who underwent epilepsy surgery in Bonn/Germany between 1988 and 2012 were evaluated.
Results: At baseline, tumor groups differed in regard to age at epilepsy onset and location within the temporal lobe. Postoperative seizure freedom was achieved most frequently (>77.8%) in DNET, GG, and DA, less often in PXA (62.5%) and the least in PA (56.5%). Preoperative memory was impaired in 67.1% of all patients, executive functions in 44.7%, and language in 45.5%. Patients with PA displayed the poorest cognitive performance. Individual significant memory decline that was observed in 27.1% of all patients was predicted by left-sided surgery, a mesial pathology, and extended hippocampal resection. Executive functions depended on antiepileptic drug (AED) load and remained stable (72.0%) or even improved (21.6%) after surgery. Language functions were unchanged in 89.5% of patients.
Conclusion: Patients with LEATs in the temporal lobe frequently show cognitive impairments. Predictors for pre- and postoperative cognition mostly correspond to what is known for temporal lobe epilepsy and resections in general. However, different tumor types appear to be associated with different cognitive and seizure outcomes with astrocytoma as the least benefitted group.

1. Introduction

Seizures are one of the most common clinical presentations of low-grade brain tumors. A specific group of those tumors possess mostly benign but highly ictal character causing drug-resistant epilepsy in many of these patients. This is why these tumors have been described as long-term epilepsy-associated tumors (LEATs) [1]. Patients usually present with rather subtle yet frequent cognitive impairment particularly of executive and memory functions [2].

The most successful treatment of seizures in these patients is the resection of the tumor aiming at the removal of the complete epileptogenic zone [3]. Therefore, in those patients, surgery is usually performed from an epileptological rather than from an oncological point of view aiming at the treatment of epilepsy. Gross total resection of the tumor, defined as no visible tumor on postoperative magnetic resonance imaging (MRI) scans, represents one of the most important prognostic factors associated with seizure freedom [3] but may bear the risk for postsurgical cognitive decline due to collateral damage to functional tissue surrounding the tumor. Patients need to be counseled with regard to this risk, however, the published basis for this is very sparse, and mostly refers to what is known to be the consequence of epilepsy surgery in general. Several studies describe cognitive functions in patients with brain tumors, but little is known about the cognitive sequelae dependent on specific tumor

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types and characteristics. Major issues of recent research were the cognitive effects of resection, radiation, and chemotherapy or the prediction of tumor recurrence. Until now, there is no comprehensive description of pre- and postsurgical cognitive functions in different types of LEAT in one cohort, and it is not clear if these functions are related to tumor histology [4] or size [5].

The present study aimed at the neuropsychological characterization of five tumor types that can be subsumed as LEATs but may differ in regard to age at onset, size, infiltration of healthy tissue, rates of malignant transformation, and seizure prognosis after respective surgery. Given the individual characteristics of different tumors, it seems conceivable that specific tumor types might be associated with different cognitive profiles and surgical outcomes.

2. Material and methods

2.1. Patients

Patients were retrospectively selected from the clinic's internal database. Informed consent was obtained in written form. All patients were adults (age > 17 yrs.) with low-grade brain tumors according to the classification of the World Health Organization (WHO) (WHO grades I and II) within the temporal lobe and had drug-resistant temporal lobe epilepsy (determined by seizure semiology, MRI, and scalp and/or invasive electroencephalography (EEG) recording). Only patients with pre- and postoperative cognitive testing were included. The first study from this center focusing on LEAT [1] – but not considering neuropsychological data – included the whole tumoral spectrum in over 200 cases and was neither limited to temporal lobe locations nor to low-grade cases and did not exclude patients under the age of 17 yrs. The following histopathologically confirmed tumor types were included: dysembryoplastic neuroepithelial tumors (DNET) WHO grade I, gangliogliomas (GG) WHO grade I, pilocytic astrocytomas (PA) WHO grade I, pleomorphic xanthoastrocytoma (PXA) WHO grade II, and diffuse astrocytomas (DA) WHO grade II. For some analyses, PXA and DA were merged as both being astrocytoma grade II tumors (A II) to achieve greater statistical power. Patients with dual pathologies (usually hippocampal sclerosis) or who had received previous treatment in terms of surgery, radiation, or chemotherapy were excluded. This resulted in a sample of 166 patients who underwent resective epilepsy surgery between 1989 and 2012 in Bonn, Germany.

Ninety percent of the patients were referred to neurosurgery after noninvasive monitoring in the Department of Epileptology, and 18% were evaluated by invasive depth, strip, and/or grid electrodes. If scalp EEG was not conclusive for determining the tumor as singular seizure onset zone, invasive EEG was performed. Tumor localization was stratified into mesial (hippocampus and/or adjacent structures as uncus, amygdala, gyrus parahippocampalis) vs. extramesial (basal, polar, lateral, or posterior). Surgery always aimed at gross total resection and was stratified in mesial lesionectomies (tailored resection of the tumor involving mesial temporal structures), extramesial lesionectomies (tailored resections sparing the mesial structures) vs. mesial or extramesial extended lesionectomies (with resection of the anterior temporal lobe of individual extent). In extramesial tumors, hippocampal structures were spared from resections. In mesial tumors, individual partial resection of the hippocampus was performed when the overall impression suggested that only parts of the hippocampus were epileptogenic — mostly according to MRI, but with additional evidence from invasive EEG (if performed), preoperative memory performance, and intraoperative evaluation.

2.2. Neuropsychological assessment

Neuropsychological examination followed a standard protocol which focused mainly on memory functions but also included intelligence quotient (IQ), language, and executive functions and has been described previously [6]. Premorbid crystallized IQ was measured with the Mehrfachwahl-Wortschatz-Test (MWT-B) [7]. Language functions were evaluated with the Token Test [8] and a phonemic verbal fluency task [9]. Verbal learning and memory was assessed by the Verbaler Lern- und Merkfähigkeitstest (VLMT) [10]. For statistical analyses, a combined score including the learning score, the delayed recall score, and the recognition score was calculated. Nonverbal memory was assessed by a revised five-trial version of the Diagnosticum für Cerebralschädigung (DCS-R) [11,12]. The number of correctly reproduced items in the last learning trial combined with the learning score (trials one through five) was combined to a DCS-R total score. For the assessment of executive functions, a response inhibition task of the cerebraler Insuffizienztest (c.IT.) [13] as well as the digit span backwards task [14] were applied.

Language as well as executive scores were merged into composite scores for each domain. Raw scores were transformed into standard scores (Mean (M) = 100, standard deviation (SD) = 10), summed up and divided by the number of considered scores resulting in the mean standard total score for the respective cognitive domain. To reduce practice effects, alternative forms were used for retesting memory after surgery.

2.3. Statistical analysis

Statistical analyses were performed with International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) 22. For detecting baseline group differences and seizure outcome, analyses of variance (ANOVAs) with post hoc tests and, in case of comparing two patient groups, t-tests were performed. Binary logistic regressions were performed for analysis of seizure outcome predictors. To determine predictors for postsurgical performance, separate multiple regressions were calculated for each cognitive domain. Categorical data were evaluated with chi^2 tests or Fisher's z-test. Categories of test performance were based on standardized test values with a performance of more than one SD below respectively above the mean classified as below respectively above average. A significant postsurgical performance change was defined as a change of more than one SD in either direction. Pearson's correlation coefficient was used to analyze the relationship between patients' characteristics and cognitive performance.

3. Results

3.1. Patients' characteristics

At baseline, the tumor groups differed significantly with regard to age at onset of epilepsy (Table 1) with the earliest onset in GG and the latest in DNET. Tumor location was mesial in > 78.6% of DNET, PA, and DA, 61.1% in GG, and only 33.3% in PXA (Fisher's exact test: $p = 0.026$, $z = 10.613$). Accordingly, hippocampal resection was performed most frequently in patients with DA and DNET and the least in patients with PXA. Side was balanced in patients with DNET, GG, and PXA; however, more than two-thirds of PA and DA were located in the left side. Groups differed significantly in tumor size (widest diameter in mm, temporally angulated MRI) with DNET > GG > PA ($p = 0.047$, $F(2) = 3.189$, $Eta^2 = 0.08$). Because of missing data, tumor sizes of patients with PXA and DA could not be considered.

3.2. Seizure outcome

Seizure freedom (Engel 1a), defined as an absence of any seizures since surgery as assessed by the routine one-year follow-up visit, was observed in 78% of all patients. Seizure outcome (Table 2) was significantly different between the groups (Fisher's z-test $p = 0.037$), with the lowest rate (56.5%) in PA, a slightly higher rate in PXA (62.5%), and the highest in DA (77.8%), GG (81.3%), and DNET (89.3%). A binary