The cognitive functions and seizure outcomes of patients with low-grade epilepsy-associated neuroepithelial tumors

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Abstract

Purpose The aim of the study was to evaluate the cognitive functions and seizure outcomes of patients with low-grade epilepsy-associated neuroepithelial tumors (LEATs).

Methods We retrospectively reviewed the clinical data of patients who underwent preoperative neuropsychological evaluations and subsequent epilepsy surgery for LEATs. The neuropsychological results of full-scaled intelligence quotient (FSIQ) and full-scaled memory quotient (FSMQ) were analyzed, as well as the postoperative seizure outcomes.

Results Of the 138 patients included in the study, 59 patients (40.4%) were female and 47 (36.6%) patients were children. Preoperatively, 138 patients received FSIQ assessments and 30 patients (21.7%) had an intellectual deficit (FSIQ < 80 scores); 124 patients received FSMQ assessments and 32 patients (25.8%) had a memory deficit (FSMQ < 80 scores). Younger age at seizure onset (OR 0.93; P = 0.035) and discordant ictal electroencephalography (EEG) findings (OR 5.26; P = 0.001) were found to predict intellectual deficits, while abnormal hippocampus (OR 2.36; P = 0.051) as well as discordant ictal EEG findings (OR 4.03; P = 0.007) tended to cause memory deficits. During postoperative follow-up, 123 patients (90.7%) were followed up at least 12 months, and among them, 105 patients (85.4%) got seizure-free (Engel class I), while 18 patients (14.6%) were not (Engel class II–IV); longer duration of epilepsy (OR 1.01; P < 0.001) and discordant interictal EEG findings (OR 5.91; P = 0.005) were found to be related to poor seizure outcomes in patients with LEATs.

Conclusion Cognitive deficits commonly occur in patients with LEATs, especially in patients with early or childhood seizures. Early surgical intervention, however, could prevent most of patients from repeated seizure onsets and thus cognitive impairments.

Keywords Epilepsy · Brain tumor · Surgery · Cognition · Seizure outcome · Risk factor

Introduction

Low-grade epilepsy-associated neuroepithelial tumors (LEATs) are rare but commonly epileptogenic brain tumors [1, 2]. LEATs grow slowly and usually develop in children or adolescents, and the glioneuronal tumors (GNTs), like ganglioglioma (GG) and dysembryoplastic neuroepithelial tumor (DNT), were the most common tumor entities in LEATs spectrum [1, 3]. In particular, most of patients with LEATs have a history of seizure onsets more than 2 years; in effect the significance of the acronym LEAT in the past was “long-term epilepsy-associated tumors” [4–6]. Due to the prevalent benign tumor features of LEATs, seizure control has become the main treatment goal. Although antiepileptic drugs (AEDs) can reduce seizures in parts of patients, the
great majority of patients would eventually become drug-resistant [3, 4, 7].

In recent years, studies have proved that surgical resection of LEATs and relevant epileptogenic foci is an effective treatment method for patients to achieve satisfactory seizure control, with a long-term rate of seizure freedom arriving at 70–90% after surgery [4, 8, 9]. Also, the related prognostic factors of seizure outcomes have been widely studied [8–11]. However, there are few reports focusing on the cognitive functions of patients with LEATs, and the cognitive impairments and related risk factors are still undefined [6, 7, 12–15]. Therefore, through this retrospective study, we aimed to evaluate the cognitive functions and their related risk factors in patients with LEATs who underwent epilepsy surgery in our epilepsy treatment center in the past decade, and meanwhile, we would explore the postoperative seizure outcomes and associated predictors to draw a comprehensive conclusion to guide clinical managements of LEATs.

Methods

Patient selection

Clinical data of patients who underwent neuropsychological evaluations and surgical treatment for LEATs between January 2008 and January 2021 at Sanbo Brain Hospital, Capital Medical University, were retrospectively reviewed. This study was approved by the Sanbo Brain Hospital Ethics Committee of Capital Medical University.

Patient selection criteria were as follows: (1) patients who had epilepsy caused by brain tumors that were histopathologically confirmed as low-grade glial or glioneuronal tumors based on the LEAT spectrum [1, 3] were enrolled in the study; but (2) patients who didn’t accept preoperative neuropsychological evaluations by Wechsler intelligence and/or memory scale, or (3) who didn’t have complete clinical data, were excluded. Finally, a total of 138 consecutive patients were included in the study.

Preoperative examination and surgical strategy

All patients underwent an individualized preoperative evaluation, including detailed medical history and physical examination, seizure semiology, electrophysiological monitoring of video electroencephalography (EEG) or magnetoencephalography (MEG) and invasive stereotactic electroencephalogram (SEEG) as needed (especially for patients with discordant findings between tumor location and seizure semiology or video EEG, or tumors invading the eloquent brain area), and imaging examinations of brain magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT) if necessary. In particular, neuropsychological evaluations were routinely recommended to patients before and after epilepsy surgery.

Brain MRI scans were performed in all patients, and the lesion size was represented by the mean maximum tumor diameter on 3-dimensional (axial, sagittal and coronal) T1-weighted MR images. Long-term video EEG monitoring was performed in all patients for at least 16 h, and the concordant EEG findings were defined as the epileptiform spike sources on interictal or ictal video EEG localized in the same brain hemisphere of tumor involvement. MEG measurements were performed in 89 (55.3%) patients with 120 min of continuous MEG data collection.

After detailed preoperative evaluations, potential surgical candidates were discussed at a multidisciplinary epilepsy surgery meeting to determine suitability for surgery, as well as the surgical plans. The aim of the operation was to remove the tumor and the relevant epileptogenic zone (EZ), which was determined by the findings of the detailed preoperative evaluations and/or intraoperative electrocorticography (ECoG). Intraoperatively, neurological electrophysiological monitoring and neuronavigation were also performed for safe tumor resection. For patients whose EZ involved the eloquent brain area, bipolar electrocoagulation (similar to multiple subpial transections), with an output power of 4–5 Watts and a cortical interval of 5 mm, was used for the remaining epileptogenic area [16]. In particular, according to whether the intraoperative ECoG and/or SEEG was performed, surgical approaches were categorized as simple tumor resection (No) and tailored tumor resection (Yes). The extent of tumor removal was determined by intraoperative observation and further confirmed by postoperative MRI examination, with no residual tumor for total tumor resection (or complete resection of tumor), less than 1/3 of tumor left for subtotal tumor resection, and otherwise for partial tumor resection.

Neuropsychological evaluation

The Wechsler adult intelligence scale (WAIS) and Wechsler intelligence scale for children (WISC), and Wechsler memory scale (WMS) were respectively performed in patients based on different age groups. The full-scale intelligence quotient (FSIQ) and the full-scale memory quotient (FSMQ) were analyzed in each patient. In particular, patients with FSIQ or FSMQ less than 80 scores were defined as having a cognitive deficit [17].

Follow-up assessment

Patients were periodically followed up at the 3rd month and 6th month postoperatively and yearly thereafter. Follow-up evaluations of surgical outcomes were performed by neurosurgeons at the clinic and/or by telephone interview. Seizure
outcomes were assessed according to the Engel classification [18], and favorable seizure outcomes were defined as Engel class I, while unfavorable seizure outcomes were Engel class II–IV at last follow-up. In addition, postoperative neuropsychological evaluations were routinely recommended to patients during each follow-up at the clinic, and the scoring results evaluated at the last time were analyzed and compared to the preoperative baseline.

**Study variable and statistical analysis**

Clinical variables of interest were evaluated for their correlations with cognitive deficits and poor seizure controls, respectively, including patient or demographic characteristics, lesion characteristics, seizure semiology and electrophysiological findings, as well as surgical factors.

Continuous variables were described with means and standard differences (SDs), while categorical variables were described with absolute and percentages. The outcome variable of cognition and seizure status was bicategorical as favorable (assigned as 0) and unfavorable (assigned as 1). Descriptive statistics between compared groups were analyzed by t tests and χ² tests for continuous and categorical variables, respectively. When necessary, the Fisher’s exact test and the Kruskal–Wallis rank-sum test were used. Variables showing a P < 0.05 in the univariate analysis were then entered into the multivariate binary logistic regression model in a forward-LR fashion. Statistical tests were considered significant if P < 0.05. Odds ratios (ORs) are presented with 95% confidence intervals (CIs). All data were analyzed using the software package of SPSS, version 21.

**Results**

**Patient demographics and lesion characteristics**

Of the 138 patients who underwent preoperative neuropsychological evaluations and subsequent epilepsy surgery, 59 patients (42.8%) were female and 47 patients (34.1%) were children (<18 years). The mean age at surgery was 21.7 ± 10.5 years (range 4–66 years), and the mean age at the first seizure onset was 12.2 ± 9.1 years (range 0.1–51 years). The mean epilepsy duration from seizure onset to surgery was 113.7 ± 105.7 months (range 1–480 months). A total of 93 patients (67.4%) had focal seizure onsets, while 45 patients (32.6%) had generalized seizure onsets, with respect to the most common seizure type in recent 1 year. In addition, 86 patients (62.3%) had a history of generalized tonic–clonic seizure (GTCS), 6 patients (4.3%) had a history of status epilepticus (SE). Seizure frequency was recorded as daily in 38 patients (27.5%), weekly in 56 patients (40.6%), monthly in 27 patients (19.6%) and quarterly or yearly in 17 patients (12.3%). A total of 97 patients (70.3%) were diagnosed as with drug-resistant epilepsy when admission (Table 1). In addition, SEEG was performed in 11 (6.8%) patients, and brain PET-CT measurements were performed in 51 (19.3%) patients.

Tumor locations in frontal, temporal, parietal, occipital, insular and multiple lobes were recorded in 16 patients (11.6%), 93 patients (67.4%), 8 patients (5.8%), 6 patients (4.3%), 2 patients (1.4%) and 13 (9.4%) patients, respectively; among them, 101 patients (73.2%) had tumors invading the temporal lobe and 66 patients (47.8%) had tumors located in the left hemisphere of brain. The mean tumor diameter was 18.4 ± 6.5 mm (range 5–37.5 mm). In addition, abnormal hippocampus (hippocampus sclerosis (HS) and/or tumor involvement) was found in 48 patients (34.8%) by postoperative histopathology. In particular, the concordant interictal and ictal EEG findings with tumor lateralization was recorded in 94 patients (68.1%) and 65 patients (47.1%), respectively (Table 1).

**Surgical and follow-up outcomes**

Tailored tumor resection by intraoperative ECoG was performed in 129 patients (93.5%). Complete tumor resection was achieved in 136 (98.6%) patients, except for 2 cases with subtotal tumor resection because of tumors invading eloquent brain areas. In particular, among the 138 patients, 82 patients (59.4%) had resection of tumor plus extralesional cortex (or hippocampus), including 76 patients with surgical approach of “Tailored tumor resection” and 6 patients with surgical approach of “Simple tumor resection”, while 56 patients (40.6%) had only tumor resection. According to postoperative pathological recordings, tumors were diagnosed as angiocentric glioma (AG) in 3 patients (2.2%), DNT in 20 patients (13.7%), GG in 105 patients (76.1%), pilocytic astrocytoma (PA) in 1 patient (0.7%), mixed GNT with GG and DNT characteristics in 6 patients (4.3%), and gliosis nodules with pathological phenotype of low-grade astrocytoma (2) and oligodendroglioma (1) in 3 patients (2.2%). In addition, a total of 41 patients (29.7%) were with postoperative histopathological finding of focal cortical dysplasia (FCD), which was relatively more common in patients with extralesional resection of tumor (34.1%) than those with single tumor resection (23.2%), but with no significance (χ² = 1.904, P = 0.168).

The mean follow-up period was 54.2 ± 33.7 months (range 3–135 months), including 9 patients (5.6%) being lost. During the follow-up, 123 patients (89.1%) were followed up at least 12 months and their seizure outcomes were evaluated by Engel classification. Finally, 105 patients (85.4%) got seizure-free (Engel class I) and among them, 53 patients (50.5%) had AEDs reduced or discontinued, while 18 patients (14.6%) still had intractable seizure onsets after
| Subtype                        | FSIQ deficit |       | P value | FSMQ deficit |       | P value |
|-------------------------------|-------------|-------|---------|--------------|-------|---------|
|                               | No          | Yes   | No. of case | No          | Yes   | No. of case |
| In total                      |             |       |         |              |       |         |
| Gender, n (%)                 |             |       |         |              |       |         |
| Male                          | 108 (78.3%) | 30 (21.7%) | 138 | 92 (74.2%) | 32 (25.8%) | 124 |
| Female                        | 62 (78.5%)  | 17 (21.5%) | 79  | 52 (72.2%) | 20 (27.8%) | 72  |
| Age at surgery, per year (mean±SD) | 22.1 ± 10.6 | 20.1 ± 10.1 | 0.342 | 22.9 ± 9.5 | 23.0 ± 12.2 | 0.947 |
| Age group, n (%)              |             |       |         |              |       |         |
| Children                      | 37 (78.7%)  | 10 (21.3%) | 47  | 27 (77.1%) | 8 (22.9%)  | 35  |
| Adult                         | 71 (78%)    | 20 (22%)   | 91  | 65 (73%)    | 24 (27%)   | 89  |
| Age at seizure onset, per year (mean±SD) | 13.3 ± 9.4 | 8.3 ± 6.3 | 0.007 | 13.8 ± 9.1 | 10.8 ± 8.8 | 0.108 |
| Epilepsy duration, per year (mean±SD) | 8.8 ± 8.6 | 11.8 ± 9.4 | 0.043 | 9.1 ± 8.6  | 12 ± 12.2  | 0.147 |
| Drug-resistant, n (%)         |             |       |         |              |       |         |
| Yes                           | 71 (73.2%)  | 26 (26.8%) | 97  | 61 (70.1%)  | 26 (29.9%) | 87  |
| No                            | 37 (90.2%)  | 4 (9.8%)    | 41  | 31 (83.8%)  | 6 (16.2%)   | 37  |
| Education level, n (%)        |             |       |         |              |       |         |
| Illiteracy                    | 3 (37.5%)   | 5 (62.5%)   | 8   | <0.001 | 0 (0%)    | 1 (100%) | 1 |
| Primary school                | 21 (67.7%)  | 10 (32.3%)  | 31  | 13 (44.8%)  | 16 (55.2%)  | 29  |
| Middle school                 | 30 (68.2%)  | 14 (31.8%)  | 44  | 29 (74.4%)  | 10 (25.6%)  | 39  |
| High or vocational school     | 37 (97.4%)  | 1 (2.6%)     | 38  | 33 (86.8%)  | 5 (13.2%)   | 38  |
| College or higher             | 17 (100%)   | 0 (0%)      | 17  | 17 (100%)  | 0 (0%)     | 17  |
| No. of AEDs when assessment, n (%) | 12 (85.7%) | 2 (14.3%)   | 14  | 0.654 | 10 (76.9%) | 3 (23.1%) | 13  |
| One type                      | 38 (80.9%)  | 9 (19.1%)    | 47  | 32 (74.4%)  | 11 (25.6%)  | 43  |
| Two types                     | 22 (68.8%)  | 10 (31.3%)  | 32  | 21 (77.8%)  | 6 (22.2%)   | 27  |
| Three or more                 | 15 (78.9%)  | 4 (21.1%)    | 19  | 12 (70.6%)  | 5 (29.4%)   | 17  |
| Unknown                       | 21 (80.8%)  | 5 (19.2%)    | 26  | 17 (70.8%)  | 7 (29.2%)   | 24  |
| Seizure type, n (%)           |             |       |         |              |       |         |
| Focal                         | 73 (78.5%)  | 20 (21.5%)  | 93  | 65 (74.7%)  | 22 (25.3%)  | 87  |
| Generalized                   | 35 (77.8%)  | 10 (22.2%)  | 45  | 27 (73%)   | 10 (27%)   | 37  |
| History of GTCS, n (%)        |             |       |         |              |       |         |
| Yes                           | 63 (73.3%)  | 23 (26.7%)  | 86  | 0.067 | 55 (71.4%) | 22 (28.6%) | 77  |
| No                            | 45 (86.5%)  | 7 (13.5%)   | 52  | 37 (78.7%)  | 10 (21.3%)  | 47  |
| History of SE, n (%)          |             |       |         |              |       |         |
| Yes                           | 6 (100%)    | 0 (0%)     | 6   | 0.416 | 5 (100%)   | 0 (0%)   | 5  |
| No                            | 102 (77.3%) | 30 (22.7%)  | 132 | 87 (73.1%)  | 32 (26.9%)  | 119 |
| Seizure frequency, n (%)      |             |       |         |              |       |         |
| Daily                         | 29 (76.3%)  | 9 (23.7%)   | 38  | 0.653 | 25 (73.5%) | 9 (26.5%) | 34  |
| Weekly                        | 43 (76.8%)  | 13 (23.2%)  | 56  | 37 (71.2%)  | 15 (28.8%)  | 52  |
| Monthly                       | 21 (77.8%)  | 6 (22.2%)   | 27  | 17 (73.9%)  | 6 (26.1%)   | 23  |
| Quarterly or yearly           | 15 (88.2%)  | 2 (11.8%)   | 17  | 13 (86.7%)  | 2 (13.3%)   | 15  |
| Lateral concordance of interictal EEG finding, n (%)<sup>a</sup> | 78 (83%) | 16 (17%)   | 94  | 0.048 | 66 (75.9%) | 21 (24.1%) | 87  |
| Concordant                    | 20 (62.5%)  | 12 (37.5%)  | 32  | 18 (64.3%)  | 10 (35.7%)  | 28  |
| Discordant                    | 10 (78.3%)  | 2 (21.7%)   | 12  | 8 (74.2%)   | 1 (25.8%)   | 9  |
| Unknown                       | 50 (84.6%)  | 10 (15.4%)  | 65  | <0.001 | 48 (80%)   | 12 (20%)  | 60  |
| Lateral concordance of ictal EEG finding, n (%)<sup>a</sup> | 15 (48.4%) | 16 (51.6%) | 31  | 13 (50%)   | 13 (50%)   | 26  |
| Concordant                    | 38 (90.5%)  | 4 (9.5%)    | 42  | 31 (81.6%)  | 7 (18.4%)   | 38  |
Neurosurgical Results

Among 138 patients with preoperative neuropsychological evaluations, 138 patients had available FSIQ results, with a mean value of 88.6 ± 17.8 scores (range 30–120 scores); among them, 30 patients (21.7%) had an IQ deficit. A total of 124 patients had available FSMQ results, with a mean value of 90.1 ± 25.4 scores (range 20–135 scores); among them, 32 patients (25.8%) had a MQ deficit. The detailed distribution of FSIQ and FSMQ were illustrated in Fig. 1.

Postoperatively, 30 patients had neuropsychological evaluations of FSIQ and 26 patients had neuropsychological evaluations of FSMQ, with a mean period of 23.9 ± 26.6 months (range 3–96 months) between surgery and final evaluation. Among 30 patients with postoperative FSIQ results, 9 patients (30%) had IQ improved, while 21 patients (70%) were unchanged (19) or got worse (2) when compared to the preoperative baseline; among 26 patients with postoperative FSMQ results, 13 patients (50%) had MQ improved, but 13 patients (50%) were unchanged (4) or worse (9) when compared to the preoperative baseline (Table 2).
Statistical analyses of cognitive and seizure outcomes

In patients with preoperative FSIQ evaluations, several variables were found to be related to IQ deficit in univariate analysis, including patient age at seizure onset (P = 0.007), duration of epilepsy (P = 0.043), drug-resistant epilepsy (P = 0.027), education level (P < 0.001), and concordance of interictal (P = 0.048) and ictal (P < 0.001) EEG findings (Table 1). Multivariate binary logistic regression analysis found that the age of seizure onset (OR 0.93; P = 0.035) and concordance of ictal EEG findings (OR 5.26; P = 0.001) were significant predictors of IQ deficits in patients. In particular, patients with younger age at seizure onset and discordant ictal EEG findings (or bilateral epileptiform discharges (EDs)) were more likely to suffer IQ deficits (Table 3).

In patients with preoperative FSMQ evaluations, several factors were found to be associated with MQ deficit in univariate analysis, which included patient education level (P < 0.001), abnormality of hippocampus (P = 0.046) and concordance of ictal EEG findings (P = 0.006) (Table 1). Multivariate logistic regression analysis found that abnormal hippocampus (HS or tumor-invading) (OR 2.36; P = 0.051)
and discordant ictal EEG findings (or bilateral EDs) (OR 4.03; P = 0.007) predicted MQ deficit (Table 3).

In particular, the postoperative FSIQ and FSMQ were closely related to the preoperative cognitive status; patients with a higher preoperative FSIQ tended to have better postoperative FSIQ ($R^2 = 0.901$, $F = 254.5$, $P < 0.001$), as well as the prediction of postoperative FSMQ ($R^2 = 0.677$, $F = 50.3$, $P < 0.001$).

By univariate logistic regression analysis, patient age at surgery (OR 1.06, $P = 0.015$), duration of epilepsy (OR 1.01, $P < 0.001$), drug-resistant epilepsy (OR 9.25, $P = 0.034$), and concordance of interictal (OR 4.23, $P = 0.009$) and ictal EEG findings (OR 4.59, $P = 0.014$) were associated with seizure outcomes. By multivariate logistic regression analysis, we found duration of epilepsy and concordance of interictal EEG findings were still related to seizure outcomes. In particular, patients with longer epilepsy duration and discordant interictal EEG findings (or bilateral EDs) were more likely to suffer poor seizure controls (Tables 4, 5).

### Discussion

Recently, surgical resection of tumors and relevant epileptogenic foci has been proved as an effective treatment method for patients with LEATs, regardless of whether they are drug-resistant or not [4, 8, 9]. The long-term postoperative seizure outcomes and related prognostic factors were also widely discussed in the literature [8–11]. However, few data can be found to be concerned with cognitive functions of patients with LEATs and related risk factors are still unknown [6, 7, 12–15].

### Cognitive functions and risk factors

Cognitive impairments commonly occur in patients with epilepsy, and approximately 20–70% of patients with seizures were reported in the literature presenting with various degrees of cognitive deficits [6, 7, 13, 15, 17, 19]. In present study, we specifically defined a cognitive deficit in patients with their neuropsychological scoring less than 80 scores, which was in line with the definition by Cormack et al. in their study [17]. We found 21.7% (30/138) of patients had an intellectual deficit, and 25.8% (32/124) of patients had a memory deficit before surgery, with their mean FSIQ and FSMQ being recorded at 88.6 ± 17.8 scores and 90.1 ± 25.4 scores, respectively.

Regarding to the risk factors, patient age at seizure onset and duration of epilepsy from seizure onset to surgery were commonly reported to be associated with cognitive deficits in patients with epilepsy [14, 17, 20–22], as well as in patients with LEATs or tumors belonging to LEATs [7, 12–15, 23], with a higher risk of cognitive deficits occurring in patients with earlier (or childhood) and prolonged seizure onsets. For example, Baxendale et al. [12] specifically evaluated 56 adults with DNT and medically intractable epilepsy and found the childhood-onset group had significantly lower scores on multiple domains of cognition, including IQ, reading, naming and verbal retention, et al., than those with an onset of seizures at the age of 12 or older; Faramand et al. [7] also reported higher preoperative FSIQ in children with epilepsy-associated GNTs of whom had an older age at seizure onset or shorter duration of epilepsy until surgery. And more specifically, Ramantani et al. [15] found children with GNTs and epilepsy duration to surgery over 4 years were at higher risk for overall cognitive impairment. Similarly, our study proved the adverse impact of younger age at seizure onset on IQ in patients with LEATs; Also, we found the same relation between IQ deficits with longer epilepsy duration but just in univariate analysis, which may be attributed to the negative correlation between age of seizure onset and duration of epilepsy in our cohort (coefficient $\beta = −3.159$; $F = 10.744$; $P = 0.001$). In general, for younger patients or children with seizure onsets, the developing brain with its immature cognitive function is more likely to be disordered by longstanding EDs in brain, which, however, less occur in adults with epilepsy [21, 22, 24–26]. Thus, early seizure control by an effective treatment, such as surgical resection,
is especially crucial to younger patients or children with LEATs [27, 28]. In particular, patient demographic features of age at surgery and gender were rarely reported to predict cognitive deficits in patients with epilepsy or with LEATs [7, 17, 21, 29].

For factor of number of AEDs or drug-resistance, many studies found that patients with more taken AEDs or with drug-resistant epilepsy had a higher risk of cognitive deficits [6, 13, 14, 22, 30]. In concordance with previous studies, we found the adverse impact of drug-resistance on IQ in

### Table 4

Univariate logistic regression analysis of clinical variables with seizure outcomes in 123 patients

| Variables                                      | B    | OR   | 95% C.I.     | P value |
|------------------------------------------------|------|------|--------------|---------|
| Female vs. male                                | 0.03 | 1.03 | 0.37–2.81    | 0.960   |
| Age at surgery, per year                       | 0.06 | 1.06 | 1.01–1.11    | 0.015*  |
| Adult vs. children                             | 0.39 | 1.47 | 0.49–4.45    | 0.491   |
| Age at seizure onset, per year                 | −0.02| 0.98 | 0.92–1.04    | 0.469   |
| Epilepsy duration, per year                    | 0.01 | 1.01 | 1.00–1.01    | <0.001* |
| Generalized vs. focal seizure                  | 0.56 | 1.74 | 0.63–4.83    | 0.283   |
| History of GTCS                                | 0.25 | 1.28 | 0.45–3.68    | 0.645   |
| History of SE                                  | 0.16 | 1.18 | 0.13–10.7    | 0.885   |
| Seizure frequency                              |      |      |              | 0.845   |
| Weekly vs. daily                               | 0.52 | 1.68 | 0.46–6.11    | 0.428   |
| Monthly vs. daily                              | 0.47 | 1.60 | 0.36–7.13    | 0.538   |
| Quarterly-yearly vs. daily                     | 0.06 | 1.07 | 0.17–6.48    | 0.944   |
| Drug-resistant epilepsy                        | 2.23 | 9.25 | 1.18–72.30   | 0.034*  |
| No. of AEDs types                              | 0.16 | 1.17 | 0.80–1.72    | 0.420   |
| Lateral concordance of interictal EEG findinga | 1.44 | 4.23 | 1.44–12.33   | 0.009   |
| Discordant vs. concordant                      | 0.07 | 0.94 | 0.15–8.30    | 0.954   |
| Unknown vs. concordant                         |      |      |              | 0.025*  |
| Lateral concordance of ictal EEG findinga      | 1.52 | 4.59 | 1.37–15.38   | 0.014   |
| Discordant vs. concordant                      |      |      |              | 0.025*  |
| Unknown vs. concordant                         | 0.18 | 1.20 | 0.30–4.79    | 0.796   |
| Tumor type                                     |      |      |              | 0.607   |
| DNT vs. other LEATs                            | 0.45 | 1.57 | 0.24–10.22   | 0.636   |
| GG vs. other LEATs                             | −0.19| 0.82 | 0.16–4.19    | 0.816   |
| Tumor side (left vs. right)                    | 0.32 | 1.37 | 0.50–3.76    | 0.535   |
| Abnormal hippocampus (HS or tumor involvement) | 0.20 | 1.22 | 0.44–3.42    | 0.705   |
| Tumor size, per mm                             | −0.01| 1.00 | 0.92–1.08    | 0.933   |
| Temporal location                              |      |      |              | 0.533   |
| Extratemporal vs. temporal                     | 0.63 | 1.88 | 0.62–5.73    | 0.268   |
| Multilobe vs. temporal                         | 0.37 | 1.44 | 0.27–7.54    | 0.666   |
| Temporal involvement                          | −0.61| 0.54 | 0.19–1.54    | 0.253   |
| Tailored resection vs. simple resection of tumora | 0.41 | 1.50 | 0.18–12.74   | 0.710   |
| Resection extent (tumor plus extralesional cortex resection vs. single tumor resection) | −0.223| 0.80 | 0.49–1.32    | 0.385   |
| Tumor-associated FCD                           | −0.051| 0.95 | 0.44–2.06    | 0.856   |
| Hospitalization, per day                       | −0.04| 0.96 | 0.90–1.02    | 0.198   |
| Follow-up, per month                           | 0.01 | 1.01 | 0.99–1.02    | 0.432   |

*AEDs* antiepileptic drugs; *CI* confidence interval; *DNT* dysembryoplastic neuroepithelial tumor; *EEG* electroencephalography; *FCD* focal cortical dysplasia; *GG* ganglioglioma; *GTCS* generalized tonic–clonic seizure; *HS* hippocampus sclerosis; *LEAT* low-grade epilepsy-associated neuroepithelial tumors; *OR* odds ratio; *SE* status epilepticus

*P < 0.05, with significance

*Patients who had unknown results in lateral concordance of interictal or ictal EEG finding with tumor lateralization were those with no epileptic discharges or normal setting on interictal EEG findings, or those with no ictus during video EEG monitoring. In particular, according to whether the intraoperative ECoG and/or SEEG was performed, surgical approaches were categorized as simple tumor resection (No) and tailored tumor resection (Yes)
Table 5 The predictors of unfavorable seizure outcomes in multivariate logistic regression model

| Predictor                              | B  | OR    | 95% C.I.     | P value |
|----------------------------------------|----|-------|--------------|---------|
| Epilepsy duration, per year            | 0.01 | 1.01 | 1.00–1.02 | <0.001 |
| Lateral concordance of interictal EEG finding | Discordant vs. concordant | 1.78 | 5.91 | 1.69–20.66 | 0.005 |
|                                        | Unknown vs. concordant | 0.41 | 1.51 | 0.15–14.81 | 0.725 |

CI confidence interval; EEG electroencephalography; OR odds ratio

our cohort by univariate analysis, but not for the number of AEDs. As it is known, AEDs are mostly neurosuppressive drugs that could suppress patient’s brain function when the drug burden is too heavy [22, 31]. Thus, if the postoperative seizure onsets are well controlled, the reduction or withdrawal of AEDs medication may partly improve the cognitive function of patients with LEATs, which has been reported by Skirrow et al. [19] who found the increase in IQ was associated with cessation of antiepileptic medication during postoperative follow-up in patients after temporal lobe surgery in childhood.

In addition, bilateral or generalized EDs on the brain may also have influence on cognitive function [13, 32, 33]. Ko et al. [13] found the presence of generalized EDs on video EEG was a significant factor associated with lower preoperative FSIQ scores in children with LEATs. Similarly, we found patients with lateral discordant EEG findings (or bilateral EDs) had lower FSIQ and FSMQ than other patients. Bilateral or generalized EDs may indicate that the brain of patients is widely affected by abnormal electrophysiological activities [33–35]. In particular, with further analysis, we found that patients with longer duration of epilepsy had a higher chance of discordant EEG findings (F = 4.04, P = 0.020). It has been speculated that patients with longer epilepsy duration are more likely to have distant or multifocal EDs [14, 21, 36]. Therefore, bilateral or generalized EDs might be as a result of the effects of prolonged seizures and directly disorder the cognitive functions of patients with epilepsy, and thus early seizure control might lower the risk of cognitive impairments in patients with LEATs.

The lateralization and localization of lesions (or epileptogenic focus) were also reported to have influence on cognitive function, and in particular, the left temporal lobe epilepsy (TLE) foci (especially the medial temporal lobe or hippocampus) are more likely to cause memory deficits than right temporal lobe [6, 12, 14, 15, 30]. However, Baxendale et al. [12] reported there were no significant localization effects (right vs. left; temporal vs. extratemporal) on any of the neuropsychological test scores in patients with epilepsy-associated DNT. Faramand et al. [7] also reported tumor location did not correlate with FSIQ outcomes in children with GNTs. In our cohort, we did not find any significant differences between tumor location and cognition deficits, except for the higher rates of memory deficits in patients with abnormal hippocampus (including HS or tumor involvement). The adverse impact of HS on cognitive function may be attributed to the large loss of neurons and limited neurogenesis in the subgranular layer of the dentate gyrus, as Paradisi et al. demonstrated [37]. In particular, when comparing the difference of extent of resection (tumor plus extralesional cortex resection vs. single tumor resection), as a surrogate of EZ extension (extralesional vs. intraleSIONal), with impact on preoperative cognitive functions, we didn’t find any significant difference, as well as tumor-associated FCD (Table 1).

Previous studies have also reported that education level has an impact on overall cognitive performance of subjects [38–40], which was also found in our cohort of whom with higher academic achievement often obtained higher FSIQ and FSMQ. However, as Phuong et al. [30] said, it is difficult to determine how cognitive performances of patients with epilepsy and their education level impact each other, because repeated seizure onsets often stop children from schooling due to varieties of reasons that may partly include cognitive or psychiatric comorbidities related to epilepsy itself [40, 41]. Therefore, we finally didn’t take the education level into the multivariate analysis of predictors of cognitive outcomes, but we believe an active education to some extent is still important to reduce the cognitive decline of patients with epilepsy (especially for children) or patients requiring postoperative rehabilitation [42–45].

Other factors of seizure semiology (such as seizure type or frequency) and lesion characteristics (such as tumor types or tumor size) were rarely reported to impact patient’s preoperative cognitive functions [6, 13, 17, 20, 30]. However, we didn’t find any correlations of these clinical factors with cognitive deficits in our cohort of LEATs patients.

With respect to the postoperative cognitive outcomes, many studies have reported that epilepsy surgery would not increase cognitive impairments of patients, and in particular, postoperative cognitive outcomes were significantly depended on the preoperative cognitive status in patients with LEATs [7, 13, 15]. Ramantani et al. [15] found postsurgical overall cognitive functioning in children with epilepsy-associated GNTs were strongly correlated with presurgical cognitive functioning that in turn was markedly influenced by epilepsy duration. However, Faramand et al. [7] only found postoperative FSIQ was significantly influenced by preoperative FSIQ in children with GNTs, while duration of epilepsy and age at seizure onset did not significantly predict postoperative FSIQ. Other factors, including the site of surgical resection and the extent of resection, had been but less reported to be associated with cognitive impairments [7, 13, 19]. We also found postoperative FSIQ and FSMQ
were closely influenced by preoperative FSIQ and FSMQ, respectively (FSIQ: $R^2 = 0.901$, $F = 254.5$, $P < 0.001$; FSMQ: $R^2 = 0.677$, $F = 50.3$, $P < 0.001$), but we did not further analyze the association of postoperative FSIQ or FSMQ deficits with other clinical factors, such as seizure freedom and discontinuation of AEDs, due to the discordant assessment time of seizure outcome (at least 12 months) and postoperative cognition (range 3–96 month) in our limited number of patients (30 cases) who underwent postoperative FSIQ/FSMQ evaluations.

In particular, some scholars believe that the improvement of cognitive function in early period after operation is not obvious, and a significant improvement requires long-term clinical observation after surgery [13, 19]. For example, Ko et al. [13] found in children with LEATs that although the postoperative FSIQ was significantly influenced by preoperative FSIQ (coefficient $\beta = 0.790$, $P < 0.001$), the median change from preoperative to postoperative FSIQ was 0.0 (range – 5.8 to 14.0) when patients were evaluated at median of 21.0 (range 13.2–31.0) months after the surgery. By contrast, Skirrow et al. [19] found a significant increase in IQ was found in patients with temporal lobe resection for HS or DNTs after an extended follow-up period of > 5 years. In present study, despite the short-term postoperative observation period in our surgical cohort of a mean time of 24 months (range 3–96 months), we have yet found a part of cognitive improvements of intelligence and memory function in 30% and 50% of patients, respectively.

Seizure outcomes and predictors

In recent years, many studies have proved that surgical resection of LEATs and relevant epileptogenic foci could help most of patients achieve satisfactory postoperative seizure control, and approximately 70–90% of patients could get seizure-free after epilepsy surgery [6, 7, 13]. In line with previous studies, we found 85.4% of patients in our cohort who were followed up at least 12 months got seizure-free and half of them (50.5%) had AEDs reduced or discontinued. However, there still were a part of patients (14.6%) with seizures uncontrolled; further analysis in our cohort found that patients with longer duration of epilepsy and discordant interictal EEG findings (or bilateral EDs) tended to had poor seizure outcomes after surgery.

Previous studies have also found that the duration of epilepsy is a risk factor for postoperative epilepsy prognosis in patients with LEATs, and early surgical resection was thus advised to achieve better seizure outcomes [7, 13]. Discordant EEG findings (or bilateral EDs) suggest that simple tumor resection couldn’t effectively control seizures [4, 13, 15]. It is worth noting that despite the discordant findings of the preoperative EEG with tumor locations in our cohort, 69% of these patients (20/29) still got seizure-free after surgery; and thus, surgical resection can also be recommended to obtain seizure freedom in nearly 2/3 of those patients. Other risk factors, such as age at surgery but at seizure onset, drug-resistant epilepsy, incomplete tumor resection, and early postoperative seizures or EDs, et al., have also been dispersedly reported in different surgical cohorts to be associated with postoperative seizure outcomes in LEAT patients [6, 7, 13–15, 20, 23], but none of associations were found in our study.

Limitations

The evidence from our study with LEATs cohort may compromise its retrospective nature and small sample size, especially the small number of patients with postoperative neuropsychological assessments. In addition, we just analyzed the general IQ and MQ without all specific domains of cognitive function. Even so, our results could also partly complement the undefined domains of the cognitive and seizure outcomes in patients with LEATs. In the future, a large, prospective and well-matched surgical cohort of LEATs from multiple epilepsy centers is still needed to get more comprehensive evidences concerning cognitive and seizure outcomes to guide the clinical treatment of patients with LEATs.

Conclusion

The preoperative cognitive impairments were commonly found in patients with LEATs, and clinical factors of older age at seizure onset, abnormal hippocampus and discordant EEG findings were adverse predictors of preoperative intellectual or memory deficits. Postoperative cognitive function was closely depended on the preoperative cognitive status of patients. Patients with LEATs could obtain satisfactory seizure control after surgery, as well as withdrawal of AEDs. However, poor postoperative seizure outcomes were often found in patients with longer epilepsy duration and discordant EEG findings. Therefore, early surgical intervention is necessary for patients with LAETs to achieve satisfactory seizure control, as well as less cognitive impairments.

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Data availability The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethical approval The Research Ethics Committee of Sanbo Brain Hospital approved the study. The manuscript does not contain individual clinical data, and informed consent was not required.

Consent to participate Not applicable.

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