Relation Between ILAE Hippocampal Sclerosis Classification and Clinical Findings in Temporal Lobe Epilepsy

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ABSTRACT

AIM: To investigate the relationship between clinical features and prognosis of the hippocampal sclerosis (HS) cases and International League Against Epilepsy (ILAE) histopathology classification.

MATERIAL and METHODS: A hundred patients with refractory epilepsy who were operated with the diagnosis of the Mesial Temporal Lobe Epilepsy were included in the study. Socio-demographic characteristics, clinical and family histories, post-operative ILAE and Engel epilepsy scores and diagnostic tests were recorded. At the same time, all of the pathological specimens were classified according to the new semi-quantitative ILAE classification. A significant statistical relationship was investigated between clinical data and HS-ILAE groups.

RESULTS: There were 36 male 64 female patients. The mean follow-up period was 6.5 years. 75% of the cases were HS-ILAE type 1, 19% HS-ILAE type 2, 6% were unidentifiable. FCD3A was detected in 3 patients. The HS-ILAE Type 2 ratio was high on the right-sided cases. In addition, HS-ILAE Type 1 ratio was high in patients with early seizure onset and long duration of epilepsy. There was no significant relationship between long-term ILAE and Engel epilepsy outcome scores and HS-ILAE types.

CONCLUSION: Resection of mesiotemporal structures in hippocampal sclerosis provides seizure control in at least two-thirds of cases. Histopathological findings may help us understand the epileptogenicity-prognosis of HS. The relationship between ILAE histopathology classification and clinical factors will become more obvious in the future. According to our study, there was a relationship between onset age of epilepsy, epilepsy duration, lesion side and HS-ILAE types. The reinforcement of these relationships with larger series will benefit clinicians.

KEYWORDS: Hippocampal Sclerosis, Epilepsy, Temporal Lobectomy, ILAE Classification

ABBREVIATIONS: CA: Cornu amonis, **DNET:** Disembryoplastic neuroepithelial tumor, **EEG:** Electroencephalography, **FCD:** Focal cortical dysplasia, **HS-ILAE:** ILAE histopathological hippocampal sclerosis classification, **HS:** Hippocampal sclerosis, **ILAE:** International league against epilepsy, **IPI:** Initial precipitating insults, **MRI:** Magnetic resonance ımaging, **MTLE:** Mesial temporal lobe epilepsy, **MTS:** Mesial temporal sclerosis, **NPT:** Neuropsychological test, **PET-CT:** Positron emission tomography–computed tomography

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■ INTRODUCTION

Epilepsy is a very common neurological disease that has a prevalence of 0.5-1% according to the World Health Organization, and is detected in approximately 50 million people. Temporal lobe epilepsies are substantial in the etiology of drug resistant epilepsy. Approximately 22% of all seizures, and 60% of partial seizures are caused by temporal lobes (15). Although the pathologies of this region are very varied, Hippocampal Sclerosis (HS) or Mesial Temporal Sclerosis (MTS) are the most common ones with unique characteristics. HS is considered a prototype for drug-resistant mesial temporal lobe epilepsies.

Hippocampal sclerosis has its own semiology and clinical course. After an effective respective surgery, full seizure control is achieved at a rate of 60-90% (7). HS is characterized with histopathological neuron loss and gliosis. The International League Against Epilepsy (ILAE) subcommittee presented a histopathological hippocampal sclerosis classification in 2013 (2). According to this classification, HS is histopathologically divided into three basic types, and three HS-related subtypes were also added, which are HS-ILAE Type 1 (typical), HS-ILAE Type 2-3 (atypical), No-HS (reactive gliosis only), Fragmented-HS (not excised *en bloc*), and FCD 3A (detection of focal cortical dysplasia with HS). Basically, the classification is mace according to anatomically sub-segments of the hippocampus; Cornu Amonis (CA1-4), Dentat Gyrus, fimbria, subiculum, parasubiculum, and entorhinal cortex based on degrees of cell loss.

The number of studies comparing ILAE classification and clinical findings and outcomes are limited. We aimed to compare the clinical, demographic and post-operative characteristics of 100 patients we operated due to HS with HS-ILAE Types.

■ MATERIAL and METHODS

Study population

This study was approved by the local ethic committee of the University of Health Sciences (Date: 06.03.2018; number: 149).

The study population was selected from among 125 patients diagnosed with drug resistant MTLE (Mesial Temporal Lobe Epilepsy) and treated surgically between 2009 and 2019. A total of 100 patients who met the inclusion criteria were included in the study (Table I). Preoperative clinical evaluations of

the cases, the ages, genders, seizure start times, presence of first triggering event, anti-epileptics used, MRI, PET-CT, Video EEG, Neuropsychological Test Batteries were recorded. All patients underwent Anteromedial temporal lobectomy (Corticoamigdalohippocampectomy). The structures were excised by a single surgeon with microsurgery as en-bloc. The patients were re-evaluated face-to-face or with teleconference in 2019, and whether they had seizures, Engel and ILAE epilepsy scores were recorded (5,19). The age, gender, epilepsy duration, epilepsy initial age, lesion side, MRI, Video-EEG, NPT (Neuropsychological Test), and PET-CT Lateralization, presence of the initial precipitating insults (IPI) (Febrile Convulsion, Neuro-infection, Trauma), history of epilepsy in first-degree relatives and dual pathologies of the patients were listed. The Engel and ILAE epilepsy scores of the patients in the 6th month after the surgery and at last follow-up were also recorded. The epilepsy scores for 2019 were evaluated both alone and by being separating into good and poor prognosis groups.

Preparation of Tissues

The paraffin blocks of the tissues were taken from the archives for re-examination, and appropriate tissues were identified for immunohistochemical examination. A section was prepared for HE staining from the paraffin blocks to examine. In addition, 3-5 μm thick parts were prepared to be a section according to the number planned for immunohistochemical examination. The sections that would be used in the immunohistochemistry method were taken to positively charged slides. The prepared slides were dried and fixed in 56°C incubator overnight.

Measurement Method

Immunohistochemical procedures were performed on 100 HS cases as previously stated (1,2). Neun, Neurofilament, and ps6 were applied to all cases that were considered to be FCD. Olig-2, IDH-1, CD34, and Neurofilament were studied to support the diagnosis in tumor cases. A ps6 was studied for a tumor case. Luxol Fast Blue was applied for hippocampal sclerosis evaluation. Neuronal loss zones were detected under 40x magnification.

ILAE Classification Method

The classification was carried out as stated in the ILAE commission report (2). In all CA1-4 hippocampal segments, common cell loss, and gliosis HS-ILAE Type 1, CA1 dominant cell loss HS-ILAE Type 2, CA4 dominant cell loss were considered as HS-ILAE Type 3. In case detecting Focal Cortical Dysplasia coexistence, the classification was made

Table I: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1- Operated in 2009-2019 by a single surgeon.	1- The suspected diagnosis of hippocampal sclerosis
2- Applying Video-EEG monitoring, T2 and T2 Flair MRI, PET-CT, Neuropsychological Test Batteries before the operation.	2- Irregular follow-up
3- Diagnosing unilateral MTLE	
4- Having regular follow-up and data recording per 6 months	

as FCD-3A, and in case no other findings were found except for reactive gliosis, the classification was made as no-HS. The tissues that were not excised en-block during surgery were considered as fragmented-HS.

Statistical Analysis

The SPSS 24 for Mac was used for statistical analysis while the findings obtained in the study were evaluated.

The Fisher Exact Chi-Square test was used since the expected frequencies were not met in comparing qualitative data.

In variables where parametric assumptions were met in comparing more than two groups, the One-Way ANOVA and Post Hoc Bonferroni were used; in variables where the parametric assumptions were not met, the Kruskal-Wallis test was used, and to determine the source of the difference, the Bonferroni Corrected Dunn Test was used.

The Bonferroni Correction was used where necessary, and the results of all other analyses except this correction were evaluated significant at $p < 0.05$ and $p < 0.01$.

■ RESULTS

A total of 100 patients were included in the study, and 64 of them were women, and 36 were male. The mean age was 30 years [11-54]. The mean follow-up period of the patients was 6.5 years [1-13]. A total of 46 (46%) of the patients who participated in the study had lesions on the left, and 54 (54%) on the right side.

The MRI revealed hippocampal sclerosis signs in the left side in 46 patients, and on the right side in 52, while 1 patient had bilateral hippocampal sclerosis. One patient had no MRI findings. Other tests are shown in Table II.

The MRI, Video-EEG, NPT findings of 65 (65%) patients showed epileptogenic focus in the same mesial temporal side. We considered this a triple accordance. A total of 30 of these (30%) were on the left, and 35 (35%) were on the right.

When the characteristics that might be the IPI in patients' past, there were 47 (47%) patients with a history of early Febrile convulsion, 32 (32%) a history of trauma, 5 (5%) had central nervous system infection, and 16 (16%) had a history of epilepsy in first-degree relatives (Table II).

Dual pathology was detected in 10 (10%) of the patients in pathological evaluations, and 3 (3%) of these were reported as Focal Cortical Dysplasia (FCD3A), 2 (2%) as Disembryoplastic Neuroepithelial Tumor (DNET), 4 (4%) as Ganglioglioma, and 1 (1%) Grade 2 Astrocytoma. All patients who were identified as FCD 3A were evaluated as ILAE Type 1.

According to Engel Epilepsy Classification in the follow-ups in the first sixth month after the surgeries, the patient distribution was; Engel 1A: 95, Engel 1B: 1, Engel 1D: 1, Engel 2B:1, Engel 3A: 1, Engel 4B:1. According to the scoring of ILAE epilepsy for the first six months, the number of patients was ILAE 1: 95, ILAE 3: 3, ILAE 4: 1, ILAE 5: 1.

In the final follow-ups (the average follow-up period was 6.5 years) for 2019, the same results were; Engel 1A: 76, Engel 1B: 4, Engel 1C: 3, Engel 1D: 8, Engel 2A: 5, Engel 2B:1, Engel 3A: 2, Engel 4B:1 and ILAE 1: 81, ILAE 3: 16, ILAE 4: 2, ILAE 5: 1 (Figure 1).

Table II: Demographic Features (n=100)

Characteristic	n (%), Means, ± SD, (min-max)
Gender (Female/Male)	64 (64) / 36 (36)
Mean age at surgery (years)	29.99 ± 8.95 (11-54)
Epilepsy duration (years)	16.97 ± 8.74 (2-45)
First seizure age (years)	13.02 ± 8.96 1-38
24h-VEEG R/L/B	53 (53) / 46 (46) / 1 (1)
MRI R/L/B/N	52 (52) / 46 (46) / 1 (1) / 1 (1)
NPT R/L/B/N/Menthal Retardation	41 (41) / 34 (34) / 18 (18) / 5 (5) / 2 (2)
PET-CT R/L/N	19 (19) / 13 (13) / 2 (2)
Side of operation R/L	54 (54) / 46 (46)
Febrile seizure history	47 (47)
Trauma history	32 (32)
Infection history	5 (5)
Family History	16 (16)

*SD: Standard deviation, **VEEG:** Video EEG, **NPT:** Neuropsychological test batteries, **MRI:** Magnetic resonance imaging, **PET-CT:** Positron emission tomography–computed tomography. **R:** Right, **L:** Left, **B:** Bilateral, **N:** normal, **n:** Samples.*
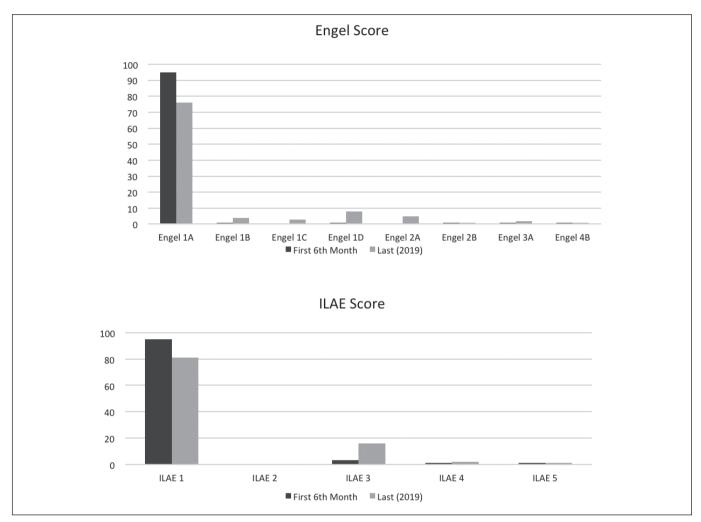
Figure 1: Follow-up of patients according to Engel and ILAE epilepsy classifications.

According to ILAE Pathology Classification, 75 (75%) patients were Type 1 ILAE, and the number of patients with Type 2 was 19 (19%) Six (6%) patients were evaluated as unidentifiable. The unidentifiable finding will be addressed in the discussion.

No statistically significant differences were detected between the groups in terms of age and gender variables.

A statistically significant difference was detected between ILAE pathology classification groups in terms of seizure age variable. The seizure starting date of those who were ILAE Type1 was lower at a statistically significant level than that of ILAE Type 2 (p<0.05).

In terms of the duration of the disease, there was a significant difference between the groups (p<0.05). The duration of the disease of ILAE Type 1 individuals was higher at a statistically significant level than that of ILAE Type 2 individuals (p<0.05).

The ILAE Pathology Classification groups were compared in terms of clinical features of the background and variables related to the IPI, and no statistically significant differences were detected between the groups (Table II).

When the patients were compared according to ILAE Pathology Classification Types, a statistically significant difference was observed between the groups in terms of the side of the lesion variable (p<0.05). In this respect, the rate of those who had lesions on the right side in the ILAE Pathology Classification Type 2 Group was higher than Type 1 (z=-2.31, p<0.05) and the Unidentifiable ones (z=-2.08, p<0.05).

There were no associations between the results based on other diagnostic tests and the ILAE HS histopathological types. When the patients were compared according to ILAE Pathology Classification types, there were no statistically significant differences between the groups in terms of final follow-up Engel scoring prognosis variables (p>0.05). This group was evaluated firstly according to good and then according to poor prognosis groups one by one, and two additional groups were added to the test and were tested separately. In the first comparison, although the good prognosis group was identified as Engel 1, and the poor prognosis group was identified as Engel 2, 3, 4, Engel 1 and 2 were accepted to the good prognosis, and Engel 3, 4 groups were accepted to the poor prognosis in the second

comparison. In the first group, the target was to separate a subgroup that did not create complete disability, which could be considered almost seizure-free, from others. In the second group; however, our target was to distinguish the group without seizures or severely reduced seizures that benefited from the surgery, separating the group from the cases that did not benefit from the surgery or increased the number of seizures, making a distinction in the form of good and poor outcomes. The subclasses A, B, C, D of Engel scoring were not included in the comparison.

When the patients were compared according to ILAE Pathology Classification types, no statistically significant differences were detected between the groups in terms of recent ILAE Epilepsy scoring prognosis variables (p>0.05). In this group, two different subgroups were created, including the good prognosis group (ILAE 1-2), and the poor prognosis group (ILAE 3-4-5-6). The target was to distinguish patients who lived without seizures or had only auras from other patients who had seizures. No significant differences were detected in this group (Table III).

■ DISCUSSION

The MTLE is the most classic type of drug-resistant epilepsy, and the most common histopathology among these is hippocampal sclerosis. The main questions are whether these cases will benefit from surgery and whether they will be better in functional terms. It is important that etiopathogenetic differences can be important, and based on this, the preoperative surgical outcome can be predicted.

The ILAE histopathology classification published in 2013 has been included in routine hippocampal sclerosis assessment by many neuro-pathologists (2). This quantitative method will help standardize the outcomes, and establish clinical-pathological relations. Since the classification was developed, clinicians started to investigate whether there was a link between clinical features and histopathology. If strong prognostic and clinical associations are detected in this way, surgical *en bloc* excision may become routine.

In our study, the histopathological examinations and surgeries were re-evaluated by one single pathologist and one single surgeon, which ensured that the whole group was quite homogeneous. When the histopathological types were evaluated, it was found that Type 1 was the most common group in the literature, and accounted for more than half of the cases (60-80%). Type 2; however, was found as the second most common in the literature between 5% and 10%. It is detected in less than 10% in Type 3 cases. The FCD Type 3A cases in which focal cortical dysplasia were detected and also were reported in quite varying rates in the literature. In the series of Gales et al., it was reported to be observed at a rate of 79% (9).

When the rates in our study were evaluated, similar rates were found in the literature (2,3). Type1 (75%), Type 2 (19%), FCD Type 3A (3%) and Unidentified (6%). Although it is interesting that there were no patients in the group classified as Type 3 in our study, we see that Type 3 patients are limited to only a few patients in some series.

The dual pathologies that accompany the pathological diagnosis of hippocampal sclerosis are also very important because of their effects on postoperative results. It can be considered that there is an effect of dual pathologies in patient groups with no adequate seizure control during the

Table III: Comparing with HS-ILAE Classification and Patients' Features

N=100	HS-ILAE Type 1	HS-ILAE Type 2	HS-ILAE Unidentifiable	p
Age (Mean±SD)	29.7 ± 9.38	30.10 ± 7.08	33.16 ± 9.55	0.664
Gender				
Female n (%)	47 (62.7)	13 (68.4)	4 (66.7)	
Male n (%)	28 (37.3)	6 (31.6)	2 (33.3)	0.930
First Seizure Age (Mean±SD)	11.80 ± 8.47	17.63 ± 8.53	13.67 ± 12.73	**0.034***
Epilepsy Duration (Mean±SD)	17.90 ± 9.15	12.47 ± 5.59	19.50 ± 7.86	**0.039***
Febrile Seizure n (%)	40 (53.3)	6 (31.6)	1 (16.7)	0,07
Trauma n (%)	25 (33.3)	5 (26.3)	2 (33.3)	0.927
Infection n (%)	3 (4)	2 (10.5)	0 (0)	0.464
Family History n (%)	11 (14.7)	5 (26.3)	0 (0)	0.275
Operation Side				
R	38 (50.7)	4 (21.1)	4 (66.7)	**0.034***
L	37 (29.3)	15 (78.9)	2 (33.3)	

SD: Standard Deviation, R: Right, L: Left, n: Samples.

Table IV: Comparing with HS-ILAE Classification and Prognosis Scores (n=100)

Classification and Prognosis Score		ILAE Type 1 (n=75)	ILAE Type 2 (n=19)	ILAE Non-type (n=6)		
		n (%)	n (%)	n (%)	c²	p
Engel Score	1	69 (92.0)	17 (89.5)	5 (83.3)	7.174	0.331
	2	4 (5.3)	2 (10.5)	0 (0.0)		
	3	1 (1.3)	0 (0.0)	1 (16.7)		
	4	1 (1.3)	0 (0.0)	0 (0.0)		
Prognosis Group 1	Good Prognosis (Engel Score 1)	69 (92.0)	17 (89.5)	5 (83.3)	1.320	0.534
	Poor Prognosis (Engel Score 2-3-4)	6 (8.0)	2 (10.5)	1 (16.7)		
Prognosis Group 2	Good Prognosis (Engel Score 1-2)	73 (97.3)	19 (100)	5 (83.3)	3.496	0.256
	Poor Prognosis (Engel Score 3-4)	2 (2.7)	0 (0.0)	1 (16.7)		
ILAE Epilepsy Score	1	60 (80.0)	16 (84.2)	5 (83.3)	6.606	0.383
	3	13 (17.3)	3 (15.8)	0 (0.0)		
	4	1 (1.3)	0 (0.0)	1 (16.7)		
	5	1 (1.3)	0 (0.0)	0 (0.0)		
ILAE Epilepsy Score Prognosis Group	Good Prognosis (ILAE Score 1-2)	60 (80.0)	16 (84.2)	5 (83.3)	0.221	1.000
	Poor Prognosis (ILAE Score 3-6)	15 (20.0)	3 (15.8)	1 (16.7)		

postoperative period. Therefore, as seen in our study; we think that instead of the excision of mesial temporal structures alone, the excision of mesial temporal structures with anterior temporal lobectomy would be more successful.

In the present study, the starting age of the disease was lower in the ILAE Type 1 group. Also, the duration of life with seizures before the surgical procedure was significantly longer with the HS-ILAE Type 1 group. This finding is also supported in a limited number of studies (4).

The patients with febrile convulsion, trauma and infection were evaluated in the background as the IPI in our study. In addition, patients with epilepsy in their family history were also evaluated in terms of having relations with ILAE pathology classification. This definition was identified as diseases like febrile seizures, meningitis, anoxia, trauma, birth trauma, intracerebral hematoma, which caused seizures that developed before the first 5 years of life, and it was argued that they could be in 40-60% of epileptic cases (11). Na et al. showed that patients with an IPI, which was described as a history of initial precipitating insults, had an association with HS-ILA Type 1 (12). It was reported that this condition is associated with the SCN1A gene mutation and the Granular Cell Proliferation occurring after the IPI. (8,10) A significant difference was not detected between these groups in our study. Although it was found that the febrile convulsion history

was more frequent in Type 1 patient groups, which was similar to the literature, this trend did not reach significance level in statistical terms. There were no clear correlations between epilepsy and family history.

A very interesting finding in our study was the correlation between the hemispheric side, in which hippocampal sclerosis was detected, and ILAE pathological classification. In approximately 79% of patients diagnosed with Type 2 based on the ILAE histopathological classification, the focus was on the right side, while in about 51% of the patients with Type 1 the focus was on the left side. This difference was statistically significant and was evaluated previously in the literature, and no significant results were found (4). Our study is the first one to detect a significant relation between the lesion side and the HS-ILAE subgroups. We could not explain this significance.

In the literature, it was reported that seizure-free life rates were between 75-85%, and 40-50% in 10-year follow-ups in the first 1-2 years (6,13). It is undeniable that the amygdalohippocampectomy surgery in HS is more successful in drug-resistant temporal lobe epilepsy in appropriate cases than medical treatment. As seen in our series, full seizure control was achieved in 95% in the first 6-month follow-ups, and 76% of long-term follow-ups (mean 6.5 years) (Engel, 1A). When compared with the previous study conducted by Tugcu et al. with the same case group, the percentage of the patients

without seizures increased for the first six months, which might be related to the increased experience of the surgical team (18). We assume that providing a higher seizure-free life than in the literature may be related with the choice of suitable patients, and the number of patients (65%) who comply with lateralization in Video-EEG, NPT and MRG findings. However, it is noted in the literature that there is no homogeneity in the evaluations of patients in terms of lack of seizures after surgery. Some studies took the Engel classification as the basis, while others based their results on ILAE surgical results score, and in a small number of studies took into account both classifications.

We examined the relation between histopathological classification by doing both outcome classifications separately, even the sub-groupings in two different ways. In this way, it was possible to make comparisons with all previous studies. Similarly, although some publications referred to a full seizure-free life as a successful result, some other studies mentioned successful results as the presence of infrequent seizures that did not create disability, and comparisons were made considering this.

In our study, no clear relations were detected between ILAE histopathological classification groups and ILAE epilepsy and Engel Epilepsy Score groups. In addition, although the good and poor prognosis groups were separated to distinguish patients who have benefited significantly from surgery, i.e. those without seizures or with a reduced number of seizures, only with auras, no significant results were detected. Gales et al. conducted a study and did not detect a significant difference; however, they also showed that recurrent epilepsy decreased in the FCD Type 3 Group (9). However, there are studies in the literature showing that the best epilepsy control is provided in HS-ILAE Type 1 group (4,12,14,17). Na et al. added that the success of the results was associated with the severity of hippocampal sclerosis. A similar correlation was also reported in the ILAE report, and it was mentioned that HS-ILAE Type 1 cases had better seizure-free life than Type 2 and 3 (60-80%) in 2-year follow-ups (2). In our study, the reason why no relation was detected between surgical results and histopathological subgroups might have been caused by HS not only being a hippocampal but also an extra hippocampal pathological condition (20). The ILAE report also mentioned that there were extra-hippocampal extensions in this area; and therefore, subgroups should be defined for more specific diagnoses. To differentiate the positive correlation from factors like surgical strategy and adequate resection, it was reported that studies with longer-term follow-ups should be conducted in wider case series (2).

This pathological classification also contains some question marks in it. A total of 6 patients were found to be unidentifiable in our study. The unidentifiable group here refers not to Fragmented-HS, but to a group that does not meet all these pathological classification criteria. The reason is that this group does not comply with the dominant neuron loss pattern in the identified subgroups. No classification proposals were made for these intermediate groups. The problem in classification stems partly from the fact that the neuron loss in ILAE classification is not quantitatively evaluated. In this respect,

Thom mentioned non-specific cases that could sometimes be included in two classes (16), which might require reworking on the classification. On the other hand, since the current classification identifies the majority of cases, the correlation between hippocampal sclerosis type and prognostic and background features can yield valuable results.

The number of cases in our study was large (n=100), and the follow-up period was long (6.5 years on average), which are acceptable levels according to the literature (15). However, the fact that there were no cases matching the ILAE Type 3 pathological classification can be considered as the limitation of the study. In the future, it may be possible to establish the relation between the findings of the background and prognostic factors with the histopathological structure in case series where HS-ILAE Type 2 and 3 and other classification groups are more. Also, the fact that the number of FCD Type 3 cases did not allow any conclusions was another limitation. In addition, the evaluation of seizure follow-ups might have been a shortcoming. As a matter of fact, there might be a correlation between memory, cognition, and psychological state and HS-ILAE types.

■ CONCLUSION

Surgical resection of medial temporal structures for drug-resistant mesial temporal lobe epilepsy is an effective intervention in appropriate cases, and is accompanied by a promising surgical result. The histopathological classification of the samples that were excised with this surgery will give us information about the course and history of the disease. More importantly, based on this information, we will have the chance to predict the surgery results of patients. As it can be seen in our study, the HS-ILAE Type 2 rate is significantly higher in early onset and long-term HS cases and in HS-ILAE Type 1 with a lesion on the right side. However, no clear associations were detected between prognostic parameters, initial triggering events, and socio-demographic variables and HS-ILAE types. As the number of cases increases, it will become more possible to clarify the clinical-pathological relations.

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