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Surgical Results of Temporal Lobe Epilepsy Based on ILAE Hippocampal Sclerosis Classification and Abnormal Immature Granule Cells are Specific to Hippocampal Sclerosis Type 1

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Abstract

Purpose: ILAE task force proposed a simple histological classification of hippocampal sclerosis. Surgical results based on this classification are presented, and significance of the presence of PSA-NCAM abnormal immature granule cells in dentate gyrusis discussed.

Methods: 41 surgical specimens are analyzed and demographic data and MRI data are carefully analyzed in terms of ILAE HS classification system. PSA-NCAM immature neurons are examined in resected hippocampus.

Results: Type 1 HS is found in 25 patients (61%). (1) types of HS doesn't correlate with age at operation and duration of illness, suggesting that these types represent distinct pathology of MTLE, (2) the mean age of onset in patients with type 1 sclerosis tends to be younger than those at least with no HS but this is not statistically significant (Kruskal-Wallis test), (3) the history of initial precipitating injury is not correlated with histological subtypes or post-operative seizure outcome, and (4) type 1 sclerosis seems to correlate with better postsurgical seizure outcome than other types. The choice of the operative procedure is important factor affecting the seizure outcome and that lateral temporal structure is also involved in the epileptogenesis in a subset of patients with MTLE. In fact, SAH alone is effective in over 80% of patients with type 1 sclerosis (Fisher's exact test, $p<0.05$) but not for patients with type 3 sclerosis.

Significance: The remarkable feature of our study is the presence of bizarre immature PSA-NCAM positive neurons in HS type 1 hippocampus. This neuron has a peculiar irregular soma with abundant neurites and synapses. The absence of bona fide astrocytes, presence of abnormal PSA-NCAM immature neurons might be neuron-glia abnormality causing long lasting intractable TLE.

Keywords: Dentate granule cells; Amygdalohippocampectomy; Temporal lobectomy; Neuron-glia abnormality; PSA-NCAM neurons 3; ILAE HS type; PSA; NCAM; Temporal lobe epilepsy

Abbreviations

ILAE: International League against Epilepsy; HS: Hippocampal Sclerosis; PSA: Polysialic Acid, NCAM: Neural Cell Adhesion Molecule; MTLE: Mesial Temporal Lobe Epilepsy; SAH: Selective Amygdalohippocampectomy

Keypoints

- In 41 TLE patients, resected hippocampiare neuropathologically classified in terms of ILAE HS classification system.
- Type 1 is observed in 25/41 (61%), and postoperative seizure control is class I: 20, class II: 2, overall seizure control 88%.
- PSA-NCAM abnormal immature neuron is detected only among HS group, [(++): two type 1, (+): two type 1, one type 3, (-): one type 2].

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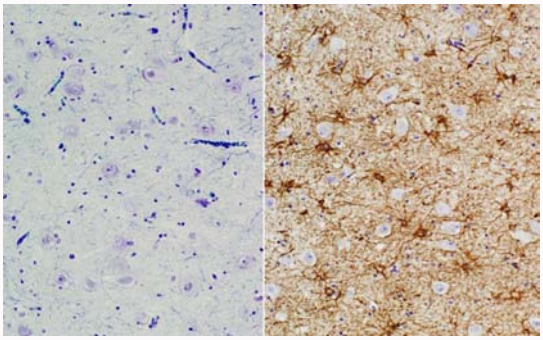

Figure 1: Amygdala sclerosis is seen in only one patient with HS Type 1 among 41 patients.

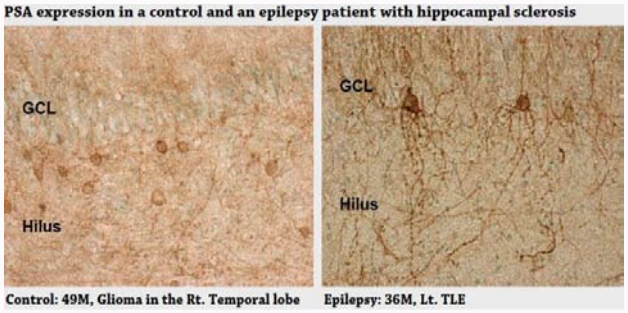

Figure 2: There are abundant abnormal-looking PSA+ cells in the dentate gyrus in HS group, particularly HS type 1 (classical type).

Introduction

International League Against Epilepsy (ILAE) classified hippocampal sclerosis (HS) into four types. Type 1 refers to severe neuronal cell loss and gliosis predominantly in CA1 and CA4 regions, compared to CA1 predominant neuronal cell loss and gliosis (HS ILAE type 2), or CA4 predominant neuronal cell loss and gliosis (HS ILAE type 3). Surgical hippocampal specimens may also show normal content of neurons with reactive gliosis only (no-HS) [1].

Since the report of the HS classification, few systematic clinical research of long-term operative results based on the ILAE HS type classification is reported [2].

Despite the strong association between HS and epilepsy, it is not clear whether the relationship is causal or it might reflect an underlying developmental abnormality. In this manuscript the long-term operative results based on the ILAE HS type classification in 41 patients to whom sub temporal Amygdalohippocampectomy (SAH) is performed will be presented [3].

Glial cells are now recognized as active communication partners in the central nervous system, and this new perspective has rekindled the question of their role in pathology [4]. They analyzed functional properties of astrocytes in hippocampal specimens from patients with mesial temporal lobe epilepsy without and with sclerosis. The hippocampus with sclerosis is completely devoid of bona fide astrocytes and gap junction coupling, whereas coupled astrocytes were abundantly present in non-sclerotic specimens. Although astrocytes dysfunction might be involved in epileptogenesis, the abnormality of neurogenesis including immature neuron should be studied especially in HS ILAE type 1 specimen [5-7].

In this clinical research, detection of immature neurons in the hippocampus among these three groups of patients are also performed to examine whether positive immature abnormal cells are specifically present in HS ILAE type 1 group.

Materials

41 surgical cases of TLE treated by SAH with or without temporal lobectomy between 1991 and 2010 are patients analyzed in this study, excluding 7 cases due to insufficient amount of tissue available for histological study. All patients were operated by a single neurosurgeon (TH).

Male to female ratio is 24 to 17, age at operation is 32.8 ± 10.8 years (9-58), age at onset is 14.7 ± 11.7 years (0-46), seizure duration is 18.4 ± 10.4 years (5-44), operation side is on the left in 23 patients, on the right in 17 patients, and not available in one patient. Postoperative follow-up ranged from 63 months to 289 months.

Table 1: Surgical procedure also seemed to be an important factor affecting the seizure outcome regardless of HS types.

HS types	Operation	n	Engel's class (n)				Efficacy (%) = Engel's class I & II	
			I	II	III	IV		
Type 1	SAH	18	14	1	3		83.3	88
	SAH & TL	7	6	1			100	
Type 2	SAH & TL	1	1				100	100
Type 3	SAH	3			2	1	0	57.1
	SAH & TL	4	3	1			100	
No HS	SAH	3	1	1	1		66.7	75
	SAH & TL	4	4				100	
Total		40	29	4	6	1	82.5	

Abbreviations: TL: Temporal Lobectomy; SAH: Selective Amygdalohippocampectomy

Table 2: HS types and preoperative MRI.

HS types	n (%)	Ammon's horn on MRI (%)		
		n	HI-signal	Atrophy
Type 1	25 (61.0)	25	23 (92.0)	19 (76.0)
Type 2	I (2.4)	1	1	0
Type 3	7 (17.1)	7	3 (42.9)	3 (42.9)
No HS	8(19.5)	7	4 (57.1)	3 (42.9)
Total	41 (100)	40	31 (77.5)	25 (62.5)

Abbreviations: HI-signal; High Intensity Signal on T2-weighted and/or FLAIR image

Among these patients, operated between 2005 to 2009 in the Department of Neurosurgery, Tokyo Women's Medical University, ten patients are selected for the neurogenesis study [7]. Control hippocampi are obtained from surgical resection of temporal lobes including medial temporal structures for complete removal of gliomas and cavernous angioma during the period (six patients), each five patients without sclerosis and six patients with HS ILAE Type 1-3 are selected for the study. Demographic data of these patients are illustrated in Table 1.

Methods

Histological evaluation was performed on formalin-fixed, paraffin-embedded tissue sections stained by Hematoxilin & Eosin and Klüver-Barrera as well as a panel of immunohistochemistry for GFAP, vimentin, NeuN, nestin, and CD34-II performed on all sections. After creating a histological ILAE classification based on

Table 3: Combined SAH & TL seems to be effective for cases with atypical MRI presentation.

HS Type	Age	Sex	Onset(y)	Seizure duration(y)	Intial Precipitating Injury	AH on MRI		Side and Operation	Postoperative period time (m) as of May 18, 2010	Postsurgical outcome (Engel's class)
						HI-signal	Atrophy			
Type 1	33	F	3	30	measles at 3y	-	+, bilat	L SH	188	II
	39	M	27	12	-	+	-	R SAH & TL	103	II
	38	F	6	32	episode of gaze and movement arrest at 4y	+, bilat	+, L	L SAH	89	III
	36	M	14	22	post traumatic seixure at 6y	+	-	L SAH & TL	75	III->I
	54	F	44	10	-	+	-	L SAH	70	I
	19	F	7	12	-	+	-	L SAH	44	III
	42	M	7	35	-	+	-	R SAH	44	I
	17	M	13	4	-	-	+	R SAH	38	I
	44	M	13	31	meaningitis at 6y	+	-	R SAH	31	III
Type 2	29	F	8	21	-	+	-	R SAH	55	III
Type 3	31	M	15	16	asphyxia, FS in infancy	-, R; +, L	+, bilat	R SAH	175	IV
	28	M	12	16	-	+	-	L SAH	89	III
	31	F	15	16	-	-, R; +, L	+	R SAH	86	III
	49	M	46	3	-	-	-	R SAH & AT	56	I
	38	M	21	17	-	-	-	L SAH & TL	42	I
	26	F	16	10	-	+	-	R SAH & TL	18	I
No HS	24	M	19	5	asphyxia	-	+	L SAH	169	I
	34	M	22	12	FS at 6y	+	-	L SAH	33	III
	34	F	28	6	-	-	-	R SAH & AT	13	I
	58	F	14	44	Seizure at 6y	+	-	R SAH & TL	5	I
	51	M	40	11	-	-	-	R SAH & TL	3	I

the distribution of neuronal loss and gliosis within the ammon's horn, the clinicopathological correlation is studied focusing on the Initial Precipitating Injury (IPI), age of onset, seizure duration, pre-operative MRI findings, operative procedure and post-surgical seizure outcome. From the neuropathological findings of 41 cases, hippocampal sclerosis are divided into three types of ILAE classification. In addition to these 3 categories, no HS category is the last classified finding. These classifications are determined by HM [1,2].

Pre-operative MRI findings are reviewed in all cases. Definition of 'typical' MRI findings is as follows, when there are both high signal change and atrophy of the hippocampus on T2 or FLAIR image. If either of these findings is lacking, such MRI findings is defined as 'atypical'. These neuroradiological features are determined by TH and HM (Table 2 and 3).

Immunohistological study: Each surgically-resected hippocampus is divided into the following samples; one of them is fixed in 4% paraformaldehyde for 3 days. Thirty-micrometer thick frozen sections were subjected to the immunofluorescence stainings for Hu, and Doublecortin and PSA. 6 Each immunoreaction is visualized by Cy2, Cy3 and Cy5, and analyzed by confocal laser scanning microscope. Immunoreaction for PSA is visualized by 3-3' Diaminobenzidine Tetrahydrochloride (DAB).

The primary antibodies used in this study includes goat anti-DCX (Santa Cruz Biotech, sc-8066, diluted at 1:2000), mouse anti-neuron-specific nuclear antigen (NeuN) (Chemicon, MAB377, 1:4000), rabbit anti-glial fibrillary acidic protein (GFAP) (Sigma-Aldrich, G9269, 1:4000) [6,7].

Results

As shown in Table 4, 25 out of 41 cases are assigned to type 1 sclerosis and constituted 61%. We find only 1 case consistent with type 2 sclerosis. 7 cases are assigned to type 3 and constituted 17%. Eight cases show well preserved histology and judged as Type 4 (no HS) and they constitute over 19%. Swelling of the remaining neurons in the sclerotic hippocampus is more frequently observed in type 1 sclerosis than other types with statistical significance (Fisher's exact test, $p<0.01$). Granule cell dispersion is also more frequently observed in type 1 sclerosis than other types with statistical significance (Fisher's exact test, $p<0.05$) (Table 4).

Demographic data of 41 patients (Table 5) show that (1) types of HS dose not correlate with age at operation and duration of illness, suggesting that these types represent distinct pathology of MTLE, (2) the mean age of onset in patients with type 1 sclerosis tends to be younger than those at least with no HS but this is not statistically significant (Kruskal-Wallis test), (3) the history of IPI is not correlated with histological subtypes or post-operative seizure outcome, and (4) type 1 sclerosis seems to correlate with better post- surgical seizure outcome than other types.

If we analyze the post-operative seizure outcome separately according to the operative procedure employed, all seven cases with Engel's class III or IV unsatisfactory seizure outcome are treated by SAH alone, while there are no such cases among 16 patients treated by combined SAH and anterior temporal lobectomy, resulting in good seizure control (Table 1). This suggests that the choice of the operative procedure is important factor affecting the seizure outcome and that

Table 4: ILAE HS type 1 is found in 25/41 (61%) patients, while amygdala sclerosis is found in only one patient, and dual pathology is found in 10/33 (30.3%).

HS types	N (%)	Ammon's horn on MRI (%)			Ammon's horn pathology (%)			Amygdala pathology (%)					Dual pathology (%)
		n	HI-signal	Atrophy	n	N-swell	GCD	n	N-swell	DG	FG	NL & G	
Type 1	25 (61.0)	25	23 (92.0)	19 (76.0)	25	24 (96.0)	24 (96.0)	21	13 (61.9)	17 (81.0)	1 (4.8)	1(4.8)	6125 (24.0)
Type 2	I (2.4)		1	0		0	1, focal		0		0	0	II 1
Type 3	7 (17.1)	7	3 (42.9)	3 (42.9)	7	1 (14.3)	4 (57.1)	6	5 (83.3)	6 (100)	0 (0.0)	0 (0.0)	3/7 (42.9)
No HS	8(19.5)	7	4 (57.1)	3 (42.9)	8	2 (25.0)	1 (12.5)	8	5 (62.5)	7 (87.5)	1 (12.5)	0 (0.0)	-
Total	41 (100)	40	31 (77.5)	25 (62.5)	41	27 (65.9)	30 (73.2)	36	23 (63.9)	31(86.1)	2 (5.6)	I (2.8)	10133 (30.3)

Abbreviations: DG: Diffuse Gliosis without significant neuronal loss, FG: Focal Gliosis, GCD: Granule Cell Dispersion; HI-signal: High Intensity Signal on T2-weighted and/or FLAIR image, N-swell: Swelling of remaining Neurons; NL & G: Neuronal Loss and Gliosis

Table 5: HS types and clinical features.

HS types	N (%)	Onset (y) Mean ± SD	Duration (y) Mean ± SD	IPI (%)	Engel's class (n)				
					I	II	III	IV	n/a
Type 1	25 (61.0)	12.0 ± 11.0	19.7 ± 10.1	17/25 (68.0)	19	2	4	0	
Type 2	I (2.4)	29	21	0/1			1		
Type 3	7 (17.1)	17.9 ± 14.0	16.1 ± 9.7	2/7 (28.6)	3	1	2	1	
No HS	8 (19.5)	22.1 ± 10.0	15.4 ± 13.2	4/6 (66.7)	5	1	1	0	1
Total	41 (100)	14.7 ± 11.7	18.4 ± 10.4	22/37 (59.5)	27	4	8	1	1

Abbreviations: IPI: Clinical History of Initial Precipitating Injury; SD: Standard Deviation

Table 6: Amygdala scrolesis is detected in only one patient with HS Type 1.

Types of hippocampal sclerosis and amygdala histopathology in patients with mesial temporal lobe epilepsy						
Histopathological findings of amygdala						
HS types	n (%)	n	Neuronal nuclear swelling and round cytoplasm	Diffuse gliosis without neuronal loss	Focal gliosis without neuronal loss	Diffuse neuronal loss and gliosis
Type 1	25 (61.0)	21	13 (61.9)	17 (81.0)	1 (4.8)	1 (4.8)
Type 2	1 (2.4)	1	0	1	0	0
Type 3	7 (17.1)	6	5 (83.3)	6 (100)	0 (0.0)	0 (0.0)
No HS	8 (19.5)	8	5 (62.5)	7 (87.5)	1 (12.5)	0 (0.0)
Total	41 (100)	36	23 (63.9)	31 (86.1)	2 (5.6)	1 (2.8)

lateral temporal structure is also involved in the epileptogenesis in a subset of patients with MTLE. In fact, SAH alone is effective in over 80% of patients with type 1 sclerosis (Fisher's exact test, $p<0.05$) but not for patients with type 3 sclerosis.

Histological evidence of hippocampal sclerosis is not correlated with pre-operative MRI findings including hippocampal high signal change on T2-weighted or FLAIR images and hippocampal atrophy, although these findings tend to be more frequently associated with type 1 sclerosis than other types; however, this is not statistically significant (Table 2).

If we take a look at the cases with unsatisfactory seizure outcome, 9 of 10 cases shows atypical MRI presentation and all cases are treated by SAH alone. However dramatic improvement of seizure control is observed after reoperation by temporal lobectomy in a couple of cases in type 1 sclerosis and one case of type 2 sclerosis. If we retrieve all 21 cases with atypical MRI presentation, post-surgical seizure outcome seems to depend on the operative procedure performed. In fact, six out of 11 patients treated by SAH alone are assigned to Engel's class III-IV, while all 10 cases treated by extensive resection resulted in favorable outcome. So, combined resection is effective for cases with atypical MRI presentation (Table 3).

We find dual pathology in about 30% of patients with hippocampal sclerosis, but there is no significant correlation between dual pathology and seizure outcome. Dual pathology is more associated with atypical MRI presentation, particularly with non-atrophic hippocampus. Although, amygdala is resected in 37 patients in our series, its sclerosis is found in only one patient (Type 1 HS) as shown in Table 6 and Figure 1. The role of amygdala in TLE is not clear in our series.

There are abundant abnormal-looking PSA positive cells in the dentate gyrus in HS group (Figure 2); particularly HS type 1 as shown in lower right panel of Figure 3. The ILAE type I HS is well correlated with the presence of abnormal PSA positive bizarre cells as shown in Table 7.

Namely, abnormal PSA (++) cells are seen in two Type 1 HS, and abnormal PSA(+) cells are seen in two Type 1 HS and one Type 3 HS, and no abnormal PSA cells are found in 6 patients of control, 5 patients of TLE without HS and one case of Type 2 HS.

Discussion

Epilepsy has for a long time been considered to be caused by dysfunctional neurons. It remains a controversial issue, whether epileptic seizures have an effect on or even increase hippocampal neurogenesis [5,6,8,9] in humans. Epileptic animal models of TLE further indicate that these newly generated neurons integrate into epileptogenic networks and contribute to increased seizure susceptibility [7,9,10,11]. Surgical specimens obtained from TLE patients represent an important tool to study mechanisms of stem

Table 7: PSA positive abnormal immature cells are seen only in TLE patients with HS, especially Type 1 patients.

Group	Age	Sex	GCD	Hilar cell Loss	Immature Cell	
					PSA+	abn PSA+
Control	49	M	(-)	(-)	(+ +)	(-)
	30	M	(-)	(-)	(+ +)	(-)
	33	M	(-)	(-)	(+ +)	(-)
	44	M	(-)	(-)	(+ +)	(-)
	16	M	(-)	(-)	(+ +)	(-)
	49	M	(-)	(-)	(+ +)	(-)
No-HS TLE	9	F	(-)	(-)	(+ +)	(-)
	37	M	(-)	(-)	(+ +)	(-)
	17	M	(-)	(-)	(+ +)	(-)
	43	M	(-)	(-)	(+ +)	(-)
	34	M	(-)	(-)	(+ +)	(-)
HS TLE	36	M	(+)	(+)	(+)	(+ +)
	40	M	(+)	(+)	(+)	(+)
	19	F	(+)	(+)	(+)	(+ +)
	42	M	(+)	(+)	(+)	(+)
	29	F	(-)	(-)	(+ +)	(-)
	35	M	(+)	(+)	(+)	(+)

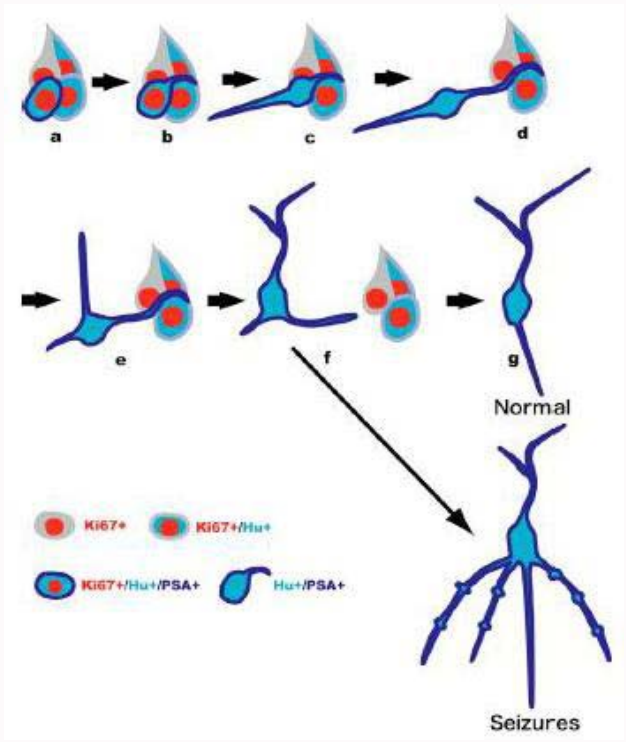

Figure 3: The presence of HS was well correlated with abnormal PSA+ bizarre cells. The role of these abnormal cells in the epileptogenesis should be clarified in the future. The difference of epileptic neuron and normal cell is schematically shown.

cell recruitment, proliferation and differentiation in the human brain [7,12-15]. In addition, increasing availability of surgical specimens opens new avenues to systematically explore disease mechanisms in chronic epilepsies [7,12].

In mesial temporal epilepsy, Hippocampal Sclerosis (HS) is the lesion most often observed [1,7,16]. In those patients studied with microelectrodes, structural MRI and histological analysis of resected hippocampal tissue shows that high rates of hippocampal fast ripples and low rates of ripples correlated with reduced hippocampal volumes and neuron densities [11,13,14,16]. The occurrence of HFOs may depend on the functional reorganization of cortical circuits rather than cell loss. Thus, the exact relationship between lesional tissue changes and the generation of HFOs is not completely understood and further studies may be required [9,11,15-18].

In this context, glial cells, astrocytes in particular, have attracted increasing attention. These cells play essential roles in brain physiology: they modulate synaptic transmission and control ion homeostasis and blood–brain barrier integrity [17,19,20]. Bedner et al., [4] have investigated coupling in astrocytes of hippocampal specimens freshly dissected from patients presenting with intractable MTLE4. They identify astrocyte uncoupling as a key event in epileptogenesis. They speculate that astrocytes have a central role in the pathogenesis of epilepsy and, have given the limited progress of neuron-centred epilepsy research over the past years.

But, epilepsy is a disease of abnormal neuronal firing, so that some neuronal abnormality specific to ILAE HS Type 11 should be studied to clarify the epileptogenesis of TLE [1,2,7,12]. In that sense, the authors focus on the detection of abnormal PSA-NCAM positive immature neurons in human hippocampus among the non-epileptic lesion group, epileptic non HS group, and epileptic HS group.

The ILAE task force proposes a system based on semi quantitative hippocampal cell loss patterns that can be applied in any histopathology laboratory1. HS ILAE Type 1, this is the most common type of HS (approximately 60% to 80% of all TLE-HS cases in reported series. The CA1 segment is most severely affected (with >80% cell loss) 1. The distribution of cell loss within segments of the hippocampus is associated with the cell loss, are signs of synaptic reorganization of excitatory and inhibitory axons 7.

It is hoped that this classification system can be used to uniformly diagnose surgical specimens of patients with TLE and provide a vehicle for collaborative studies across surgical epilepsy centers.

And neuropathological findings of medial temporal structures in 41 MTLE patients are reviewed. 25 out of 41 cases are assigned to type 1 sclerosis and constituted 61%. We find only one case consistent with type 2 sclerosis. seven cases are assigned to type 3 and constituted 17%. Eight cases show well preserved histology and judged as Type 4 (no HS) and they constitute over 19% (Table 4). And ILAE HS type 1 seemed to correlate with better postoperative seizure outcome than other types (Table 5). Surgical procedure also seems to be an important factor affecting the seizure outcome regardless of HS types, suggesting the possible role of lateral temporal structure in the epileptogenicity of MTLE (Table 1) [20-23].

There are some possible limitations in this study. First of all, the classification is solely based on the qualitative observation and may require inter-observer agreement particularly in case with subtle change. Secondary, we have only one case with type 2 sclerosis and one case with type 1 sclerosis with severe CA2 involvement. This results in some limitations in statistical analysis. And thirdly we don't encounter the case of HS with subicular involvement.

There are abundant abnormal-looking PSA positive cells in the

dentate gyrus in HS group, particularly HS type 1 (classical type) (Figure 2 and 3).

The ILAE type I HS is well correlated with the presence of abnormal PSA positive bizarre cells as shown in Table 7 [Type1 ;(++)2, (+)2, Type 2;(-)1, Type3;(+)1]. The role of these abnormal cells in the epileptogenesis should be clarified in the future [18].

This abnormal immature neuron is schematically illustrated comparing to normal PSA positive cells without epilepsy history (Figure 2 and 3). The authors propose that in addition to the abnormality of astrocytes in 10 sclerotic hippocampus, the presence of abnormal immature PSA-NCAM positive neuron is supposed to be related to intractable mesial temporal lobe epilepsy. However, the potential of human hippocampal precursor cells to differentiate into mature spiking neurons as well as electrophysiological characterization of functionally integrated human neurons remains to be shown [18,24,25].

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