

NEUROBIOLOGY

Temporal lobe epilepsy with hippocampal sclerosis – An insight into the disease entity

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Temporal lobe epilepsy with hippocampal sclerosis (HS) is considered a distinct entity due to several pathognomonic clinical features and consistent pathological substrate. However, presurgical evaluation frequently reveals variations among patients with HS. Such findings consequently raise the question whether HS is a unique electroclinical syndrome.

In 116 HS patients undergone anterior temporal resection at our institute, different ictal propagation patterns were found during their presurgical evaluation (Table 1). Among these, 80 cases (68%) have “classical mesial temporal lobe epilepsy”. The propagation of ictal scalp EEG confined only to one hemisphere ipsilateral to the lesion, with or without volume conduction to the other side. All presurgical investigations point to single epileptogenic zone congruent to the unilateral HS and surgical results are excellent. The rests (32%) show varied ictal scalp EEG propagation and carry less favorable surgical prognosis. These include subgroup with partially concordant results to MRI, SPECT or neuropsychological findings (8%), discordant results with ictal EEG lateralized to the hemisphere opposite to the HS (9%), non-lateralized or generalized ictal pattern (3%), switch of lateralization or bitemporal asynchronous ictal pattern (3%) and bilateral independent EEG lateralized to either side in different seizures (2%). Dual pathology, mostly with focal cortical dysplasia, account for 5% in our series.

Despite these variations, seizure patterns are frequently found to be stereotyped or “habitual” in each individual. Different pathogenic mechanisms have been suggested from recent evidences to underlie these different subgroups.

Unilateral hippocampal sclerosis

There are increasing evidences to support that preexisting HS being a cause of temporal lobe

epilepsy, not a consequence of repeated seizures. The severity of HS significantly correlated with age of onset but not with history of prolonged seizures and duration of epilepsy.¹ It is concluded that developing hippocampus is more susceptible to insult that cause the HS than that of the more mature individual.

The importance of hippocampal neuronal loss, gliosis and mossy fiber sprouting in ictogenesis is still unclear. One study in rats with spontaneous epilepsy after limbic status epilepticus has shown that increasing seizure frequency positively correlated with the GABAergic axon sprouting and increase in NMDA and AMPA receptor stains.² This finding may suggest some association between the morphological changes in HS and chronic seizures. However, their role in ictal generation remains to be elucidated.

Wilson has shown that ictogenesis is a result of enhanced neuronal excitability as well as enhanced inhibitory mechanism involving their specific local circuits.³ The enhanced inhibition was also demonstrated in kindled rats⁴ and could be epileptogenic by promoting hyper-synchronization.

“Fast ripples” (250-500 Hz waves) were found in dentate and entorhinal cortex of kainic acid injected rat as well as in patients with mesial temporal lobe epilepsy.⁵ These characteristic interictal potentials occur only in area generating spontaneous seizures and are suggested as the hallmark of epileptogenic region. Fast ripples were hypothesized to reflect the reverberating dentate-entorhinal circuits unique for initiating epileptic seizures. In addition, “fast ripples tail gamma complexes” (Fast ripples followed by gamma oscillation of 30-50 Hz frequency) were found in wide distribution and were mediated through GABAergic mechanism. They may be the result of maximal dentate activation which permits propagation of ictal activity to the rest of the brain.

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Table 1: Analysis of ictal scalp EEG propagation during presurgical evaluation in 116 mesial temporal lobe epilepsy patients undergone anterior temporal resection at Chulalongkorn Comprehensive Epilepsy Program from March 1999 to July 2004 (adult, age > 15)

Subgroups of HS	Scalp EEG propagation pattern	Number	Percent
HS only Completely concordant: congruent to all presurgical investigations	Ictal EEG confined only to the hemisphere ipsilateral to HS, with or without volume conduction to the other hemisphere	80	68
Partially concordant: slight disagreement with other presurgical investigations	Ictal EEG lateralized to the hemisphere ipsilateral to HS	9	8
Discordant: much disagreement with other presurgical investigations	Ictal EEG lateralized to the hemisphere contralateral to HS	11	9
	Nonlateralized or generalized ictal EEG pattern	4	3
	“Switch of lateralization” EEG pattern	3	3
	Bitemporal asynchronous EEG pattern	1	1
	Bilateral independent EEG lateralized to either side in different seizures	2	2
Dual pathology	Ictal EEG varied	6	5
Total		116	100

Data from Chulalongkorn Comprehensive Epilepsy Program (CCEP)

(The 24-hour video/EEG monitoring performed by using scalp electrodes and additional true anterior temporal electrodes according to the international standard 10-10 system electrode placement. Sphenoidal electrodes inserted in selected cases. Pz used as reference in referential montages. More than 5 seizures recorded in each patient. The video/EEG results were correlated with high resolution MRI (1.5T), ictal SPECT, Wada and neuropsychological tests in the multidisciplinary epilepsy conference.)

HS: hippocampal sclerosis

“Silent period”, an interval of time between the injury and the onset of epilepsy can usually be seen in human mesial temporal lobe epilepsy and in animal studies. In human, silent period is usually 3 to 5 years before epilepsy develops. In kainic acid treated rats, fast ripples was shown to generate in the hippocampus and the ipsilateral entorhinal cortex 11-14 days after injection, whereas spontaneous seizures occur 2-4 months after the injury.⁶ Small clusters of pathologically interconnected neurons may develop after focal injury and may be capable of generating hypersynchronous discharges which initiate epileptogenesis. As silent period progresses, a network of such clusters is formed. When the

network engages symptomatogenic brain areas, the clinical seizure occurs, ending the silent period.

The mechanism of unilateral involvement, predilection of side and degree of HS as well as its genetic influences remain to be elucidated.

Dual pathology

Dual pathology was found to be associated with cortical dysplasia, porencephalic cyst and reactive gliosis more than with tumor or AVM.⁷ The low incidence of tumor association in contrast to what reported previously, made the secondary epileptogenesis from coexisting tumor as the mechanism of HS seem doubtful. It is proposed that common pathologic mechanism during early

development may account for both mesial temporal sclerosis and concomitant lesion such as dysplasia, gliosis or porencephalic cyst.

Bilateral HS

Particular ictal EEG spreading patterns during the evolution of seizures may reflect bilateral temporal involvement. In bitemporal asynchrony and switch of lateralization, more bilateral independent interictal discharge and poorer surgical outcome were found.⁸ Bilateral hippocampal volume loss was found to be more common in patients with unilateral HS than in those without.⁹ Four young children were reported to develop bilateral HS after widespread initial etiology.¹⁰ These evidences may suggest a pathogenic connection between primary damage to both hippocampi to the pathogenesis of HS.

The individual pattern

Although semiology, ictal EEG onset and propagation as well as functional neuroimaging are different among mesial temporal lobe epilepsy variations, seizures mostly manifest in consistent pattern in the same individual. Anatomic studies suggest that local circuits in neocortex and hippocampal remodel during postnatal life to form a new set of network connections as the brain matures. Synchronized discharges of neuronal population are demonstrated to alter axon remodeling. An associated malformation may predispose the young hippocampus to excitotoxic damage in response to environmental insult such as febrile convulsion. Early seizures therefore alter the development and maintenance of neuronal connections. Remodeling of larger axonal networks capable of controlling seizures may also be disrupted. Subsequently, the epileptogenic circuits are formed and conceivably contribute to epileptogenesis. Differences in extents of primary injury and degrees of disrupted axonal plasticity during early life may explain why the electroclinical patterns are different among patients in this disease entity but consistent in the same individual.

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