

Experiences of Epilepsy Surgery in Intractable Seizures with Past History of CNS Infection

Joon-Hong Lee¹, Byung-In Lee¹, Soo-Chul Park¹, Won-Joo Kim¹,
Jeong-Yeon Kim¹, Sun-Ah Park¹, and Kyoong Huh²

We studied the clinical characteristics, location of epileptogenic regions, and the surgical outcomes in 18 patients with intractable epilepsy associated with previous CNS infections. All patients underwent an extensive presurgical evaluation and 11 patients had intracranial EEG monitoring. On the basis of presurgical evaluation, epileptic regions were localized to the mesial temporal (n=12) and the neocortical (n=6) regions. The age of the time of CNS infection was significantly younger and the latent period of non-febrile seizures after CNS infection was longer in patients with mesial temporal lobe epilepsy (MTLE). MRI showed hippocampal atrophy and hippocampal signal changes in 11 of 12 patients with MTLE. Among 6 patients with neocortical epilepsy (NE) 5 patients had normal MRI and one showed cerebral hemi-atrophy. Surgery was successful (class I & II) in all patients with MTLE, however, in the patients with neocortical epilepsy, seizure-free results were not achieved in any patients after resective surgery (6 patients) and only 2 patients achieved Class II outcomes after a second epilepsy surgery consisting of neocortical resection. Patients with MTLE after CNS infection were differentiated from the group of neocortical epilepsy by an earlier onset of CNS infection, a prolonged latent period and a higher frequency of meningitis. The characteristic pathology in this group was hippocampal sclerosis and the surgical result was excellent. Neocortical epilepsy following CNS infection usually had no focal lesion on MRI and was associated with a relatively poor surgical result. This study suggested that the surgical outcome was influenced by the type of epileptic syndromes rather than the etiology of seizures. The association of MTLE with the younger age of CNS infections and with meningitis more frequently suggested that the neocortical neurons during infancy or early childhood may be more resistant to the epileptogenesis, or that the CNS infections in patients with MTLE might be milder in severity to cause selective injuries to the hippocampal neurons during their vulnerable stage.

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Department of Neurology, Yonsei University College of Medicine, Seoul, Korea¹

Department of Neurology, Ajou University College of Medicine, Suwon, Korea²

Address reprint request to Dr. J.H. Lee, Department of Neurology, Yonsei University College of Medicine, Severance Hospital C.P.O. Box 8044, Seoul 120-752, Korea

Epilepsy is an well recognized complication following CNS infection. CNS infections often precipitate seizures or status epilepticus during their acute illness, but also cause late unprovoked seizures in a significant number of patients (Menkes, 1985). Previous epidemiological studies have shown that about 2.7-to-6.7% of epileptic patients were causatively related to previous CNS infections, with partial seizures accounting for approximately 70% of

seizures following CNS infection (Rosman *et al.* 1985; Annegers *et al.* 1988). The control of seizures, and especially of status epilepticus, during the acute stage seems to be the most effective treatment for improvement of the prognosis of acute encephalitis (Mieko *et al.* 1989). The risks of developing epilepsy may be variable to the causative organisms, the type of infections and the presence of early seizures. In general, the encephalitis was associated with higher risks of late epilepsies compared to the meningitis. The occurrence of seizures during acute illness was also an important factor increasing the risk of developing late epilepsy. Annegers *et al.* (1980) reported that the 20-year risk of late epilepsies was 22% for patients with viral encephalitis and early seizures, 10% for patients with viral encephalitis without early seizures, 13% for patients with bacterial meningitis associated with early seizures, and 2.4% for patients with bacterial meningitis without early seizures.

Epilepsies following CNS infection are often refractory to current medical treatment and these patients are often subjected to epilepsy surgery. Recently, the outcome of epilepsy surgery has improved significantly, especially in cases with temporal lobe epilepsy (TLE). The successful seizure outcome of surgery in patients with TLE associated with focal lesions or hippocampal sclerosis (HS) in MRI has been achieved in over 90% of patients (Engel *et al.* 1993; Williamson *et al.* 1993). On the other hand, the results of epilepsy surgery in cryptogenic neocortical epilepsy (NE) are still unsatisfactory with excellent outcomes being achieved only in 20-to-50% of patients. Previously, patients with intractable epilepsies related to CNS infections were considered as poor surgical candidates due to the assumption that the brain damage caused by CNS infections is often multifocal or diffuse. However, with recent developments in neuroimaging and the localizing techniques of epileptic foci, the previous concept about the relationship between CNS infection and intractable epilepsies should require further evaluation.

MATERIALS AND METHODS

Patients

We reviewed the medical records, epilepsy clinic registry forms and the data of presurgical evaluations of the patients who had epilepsy surgery at Yonsei University Medical Center from January, 1989 to December, 1995. Patients and family members were questioned extensively by multiple interviewers during presurgical evaluation and during follow-up sessions. The inclusion criteria of the study patients were as follows:

- 1) diagnosis of CNS infections was made by the physicians who cared for the patients during their febrile illnesses.
- 2) CSF examinations were carried out during the acute illnesses.
- 3) absence of other potential etiological factors for their epilepsies; i.e., focal lesions in MRI, history of significant head trauma, history of febrile convulsions or non-febrile seizures preceding the CNS infections, etc.
- 4) follow-up for more than 1 year after surgery.

We excluded patients with a history of cerebral abscesses, parasitic CNS infections or CNS infections following intracranial surgery.

Presurgical evaluation

All patients underwent the presurgical evaluation according to the protocol of YUMC, which was described previously (Engel *et al.*, 1993). Briefly, the phase I protocol consisted of neuroimaging studies (MRI, interictal and ictal SPECT), neuropsychological tests including intracarotid sodium amytal tests and scalp EEG telemetry recording using sphenoidal electrodes. At least 4 episodes of the patient's habitual seizures were recorded for each patient. In patients with inconclusive results for phase I investigation, phase II investigations were conducted by using either subdural electrodes or foramen ovale electrodes. In patients with implanted subdural electrodes, functional brain mapping by electrical stimulation was routinely performed. The results of presurgical evaluations in each patient were presented at an organized session for the decision about

surgery and to formulate the surgical procedures most appropriate to each patient.

Surgical outcome

All patients were followed at the Yonsei Epilepsy Clinic (YEC) regularly for at least one year after surgery and their surgical results were assessed by using Engel's classification (Engel *et al*, 1993); Class I : free of disabling seizures with or without early postoperative seizures (first few weeks), Class II : rare disabling seizures ("almost seizure-free"), Class III : worthwhile improvement, Class IV : no worthwhile improvement.

RESULTS

A total of 101 patients had epilepsy surgery at the Yonsei University Medical Center from January, 1989 to December, 1995, and among these patients, 12 were lesional cases, 4 had past histories of head trauma, 47 had non-specific past histories of illness and 38 had past histories of convulsions with elevated body temperature. Among 38 patients who had past histories of convulsions with elevated body temperature, a total of 18 satisfied the inclusion criteria and were included in the study. Nine patients were male and 9 were female, with a mean age of 28 years (range: 17 years to 38 years). Mean follow-up period was 22 months (range: 12 to 51 months). The mean age at the time of CNS infection was 84 months (range: 2 months to 31 years) and the mean age of onset of a non-febrile seizure was 12 years (range: 3 to 31 years). The localization of the epileptogenic region was identified as the mesial temporal region in 12 patients and the extra hippocampal neocortical regions in 6 patients. For the purpose of this study, these two groups of patients were analyzed separately.

Mesial Temporal Lobe Epilepsy (MTLE)

Twelve patients were identified as MTLE. Phase II investigations were conducted in 5 patients; foramen ovale electrodes in 1 patient, subdural electrodes in 3 patients, and both subdural and foramen

ovale electrodes in 1 patient. Unilateral hippocampal atrophy with an increased T₂ signal was the major MRI feature found in 11 of 12 patients and one of these patients showed associated ipsilateral diffuse temporal lobe atrophy. All patients underwent an anterior temporal lobectomy (ATL) with excellent results: class I in 11 patients and class II in 1 patient. Pathological features of hippocampal sclerosis were found in 11 patients, with one patient showing normal pathology.

The mean age of CNS infection in patients with MTLE was 3.21 ± 2.7 years and the latent period between CNS infection and the onset of a non-febrile seizure was 7.02 ± 4.2 years. In fact, 11 of 12 patients with MTLE developed CNS infections at the age of 6 years or younger and the remaining patient developed CNS infection at the age of 7 years. In 9 of 12 patients with MTLE, the diagnosis of previous CNS infection was meningitis, with tuberculous meningitis in 3 patients. The causative organisms of meningitis in the remaining 6 patients were not identified. Three patients were found to have encephalitis, but causative organisms were not specified.

Neocortical Epilepsy (NE)

The results of presurgical evaluation in 6 patients pointed to extrahippocampal NE. All these patients underwent phase II investigation consisting of implantation of subdural electrodes with or without foramen ovale electrodes. MRI in these patients did not show any focal abnormalities in 5 patients and left cerebral hemiatrophy in 1 patient. One patient (#13) had a right temporal lobectomy initially without improvement. She had a second operation consisting of a right frontal cortisectomy which resulted in significant improvement of seizure control (class II). The patient (#16) with the left cerebral hemiatrophy was also operated on twice. The first surgery consisted of a left anterior temporal lobectomy and a left posterior temporal cortisectomy, resulting in some, but less satisfactory improvement (class III). Further resection of the left parieto-occipital region in the second surgery was associated with significant improvement in seizure control (class II). However, the remaining 4 patients with normal MRI did not show any satisfactory improvement of seizure control.

Table 1. Patient characteristics

patients No.	Age** /Sex	Type	Infection onset	Seizure onset (yr)	MRI	Surgery	2nd.-surgery	Pathology	Outcome (Class)*
1	23/M	M	4yr	10	L Hc atrophy	L ATL		MTS	I
2	37/M	E	6yr	12	L Hc atrophy	L ATL		MTS	I
3	20/M	M	2mo	12	R Hc atrophy	R ATL		MTS	I
4	17/F	M,bac	5mo	3	R Hc atrophy	R ATL		NI	I
5	20/F	M	1yr	11	L Hc atrophy, inc T ₂	L ATL		MTS	II
6	38/M	M,Tbc	7yr	14	R Hc atrophy, inc T ₂	R ATL		MTS	I
7	26/M	M	8mo	7	L Hc atrophy	L ATL		MTS	I
8	30/F	M,Tbc	1yr	15	Inc T ₂ L Hc	L ATL		MTS	I
9	26/F	M,Tbc	6yr	6	R Hc atrophy, inc T ₂	R ATL		MTS	I
10	27/F	M	1yr	12	L T atrophy, inc T ₂ L Hc	L ATL		MTS	I
11	34/M	E	5yr	13	R T atrophy	R ATL		MTS	I
12	24/F	E	6yr	8	NI	L ATL		MTS	I
13	37/F	E	31yr	31	NI	R ATL	Partial R F cortisectomy	Gliosis	II
14	32/M	E	16yr	16	NI	L ATL, Partial L PT cortisectomy		Micro-dysgenesis	III
15	22/M	E	8yr	8	NI	L ATL, Partial L PT cortisectomy		MTS	IV
16	35/M	E	5yr	5	L hemi-atrophy	L ATL, Partial L PT cortisec.	Partial L-PO cortisec.		II
17	33/F	E	28yr	28	NI	Partial L PT, O cortisectomy, L ST MST		Micro-dysgenesis	III
18	23/F	E	9yr	9	NI	Partial T P cortisectomy, R T MST			IV

*: Classification of postoperative outcome (Engel et al. 1993)

** : Age given in years, meningitis patients listed first.
M: Meningitis.

E: Encephalitis.

M,bac: Meningitis bacterial

M,Tbc: Meningitis tuberculosis

R: Right

L: Left

T: Temporal

PT: Posterior temporal

ST: Superior temporal

O: Occipital

NI: Normal

Hc: Hippocampus

MST: Multiple subpial transection

ATL: Anterior temporal lobectomy

MTS: Mesial temporal sclerosis

rol (class III-IV) after localized neocortical resections.

The mean age of CNS infection in patients with NE was 16.17 ± 10.9 years, which was significantly older than the patients with MTLE ($P < 0.034$). The latent period of non-febrile seizure onset after CNS infections was less than one year in all patients, which was significantly shorter than the patients

with MTLE ($P < 0.005$). The types of CNS infection in all patients were identified as encephalitis without identifiable organisms.

DISCUSSION

Although epilepsies caused by previous CNS

infections are often refractory to current anti-epileptic drug therapy, the surgical results in these patients have not been systematically investigated yet. The results of our study clearly suggested that the type of seizures and their surgical results varied according to the type of CNS infections as well as the age of CNS infections. In patients presented with MTLE, meningitis was the prominent type of CNS infection and their age of febrile illness was much younger than for patients with NE. In addition, the latent period from the CNS infection to the onset of a febrile seizure was much longer in patients with MTLE. The characteristic pathology in these patients was hippocampal sclerosis (HS), which was found in 11 of 12 patients. The patient with normal pathology had, in fact, shown unilateral hippocampal atrophy in MRI, a characteristic imaging feature of HS. Because we did not conduct cell counting for the pathological diagnosis of HS, it seems possible that milder cases of mesial temporal sclerosis (MTS) might not be detected.

HS is the major pathological feature of MTLE found in 60-to-70% of surgical specimens of anterior temporal lobectomy (ATL). The etiology of HS is still controversial but the most likely hypothesis is that CNS insults in early childhood cause hippocampal injury which initiates the development of injured hippocampal neurons into epileptogenic neurons over time. The sprouting formation of abnormal neuronal mossy fibers has been demonstrated by using tim-staining, which might be evidence of the formation of abnormal neuronal circuitry important in the development of epileptogenicity. A latent period of many years from the acute CNS insults in most patients with TLE might be related to the gradual development of initial injury into the epileptogenic region.

The nature of acute CNS insults precipitating HS is quite variable (Uno *et al.* 1989; Sapolsky *et al.* 1990). Although prolonged febrile convulsion is the most frequently cited etiology of HS, head trauma, hypoxia or CNS infection at a young age are also associated with HS (Mouritzen-Dam, 1980; Sager and Oxbury, 1987).

Marks *et al.* (1992) reported that whereas patients (n=16) who developed medically intractable partial seizures following meningitis were commonly associated with mesial temporal sclerosis, most encephalitis patients (n=22) had neocortical foci, and that patients who had either encephalitis or meningitis before the age of 4 years developed MTLE associated with HS. Also, they investigated patients with intractable epilepsy caused by head injury (Marks *et al.*, 1995). Five of 25 patients were found to have MTS and all of them suffered the head injury before the age of 5 years and they became seizure-free after ATL. These findings are in agreement with our results. In our study, the mean age of CNS infections was 3.21 ± 2.7 years and only one in 12 patients had the illness at 7-years-old. Compared with that, only 1 in 6 patients with NE developed encephalitis before the age of 6 years and this patient showed diffuse left cerebral hemiatrophy in MRI, which also included left temporal and hippocampal atrophy. The remaining 5 patients showed normal MRI without any evidence of hippocampal atrophy. Therefore, the development of CNS infections at an early age, before 6 years, is prone to develop hippocampal injury which may mature into HS over a latent period of several years, and these patients can be successfully treated by ATL.

On the other hand, patients with intractable epilepsies following CNS infections after 6 years were usually found to have neocortical epilepsies, presumably caused by the direct damage to cortical neurons by causative organisms, probably scarring changes. The pathological features in these patients were either normal, gliosis or microdysgenesis, which were non-specific pathological features. The presurgical evaluations in these patients often showed multifocal or widespread interictal epileptiform discharges and were not successfully controlled by surgery despite extensive investigations using invasive electrodes. In general, the surgical results of NE without focal lesions in MRI are quite poor. The specific pathologies in cryptogenic NE are usually absent even in patients who have achieved successful seizure control after surgery. Therefore, the poor surgical results in our patients with NE were not unusual and a similar result was reported in patients with seizures related to head injury (Marks *et al.*, 1995).

Although we could not clearly identify whether the poor surgical results in patients presented with normal MRI and NE were either due to the multifocal or diffuse neuronal injuries caused by orga-

nisms, or difficulties in localizing the epileptic foci, they are usually not amenable to resective surgery and require special care in the selection of surgical candidates. On the other hand, patients with MTLE after CNS infection are clearly differentiated from patients with NE by an earlier onset of CNS infection, a prolonged latent period, the characteristic pathology of HS, meningitis as the predominant type of CNS infection, and excellent surgical results. We postulate that the mechanisms of epileptogenesis in patients with MTLE after CNS infection are different from patients with NE.

It seems possible that the neocortical neurons during infancy or early childhood may be more resistant to epileptogenesis, or that CNS infection in patients with MTLE might be milder in severity and only cause selective injuries to the hippocampal neurons during their vulnerable stage. Future prospective studies may be required to resolve the issue.

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