대 한 소 아 신 경 학 회 지
Vol. 20, No. 2, June, 2012

□원 저□

Natural History of Treated New-Onset Epilepsy in Children: A Long-term Follow-up Cohort Study in a Single Center

Won Sub Shin, M.D., Il Rak Choi, M.D.
Yu Jin Chang, M.D., Hyun Young Lee, MS*
Seung Soo Shin, M.D.* and Sung Hwan Kim, M.D.

Department of Pediatrics, Unit of Clinical Epidemiology and Biostatistics*
Ajou University School of Medicine, Suwon, Korea

= Abstract =

Purpose: Seizure outcomes are more complicated in terms of repeated remission and relapse in the course of epilepsy. We aim to investigate the different patterns of evolution in new-onset pediatric epilepsy and the seizure outcome of different types of epilepsy syndromes.

Methods: We examined the evolution pattern of remission and relapse in the course of epilepsy in 326 children who were less than 15 years of age, with new-onset epilepsy. Different remission-relapse patterns were determined in each patient and according to epilepsy syndromes. The probability of repeated remission and relapse were analyzed with Markov process.

Results: During follow-up (mean±SD: 79±25 months) of 326 patients, early remission, defined as remission within the first year of treatment, was seen in 288 patients (88.4%), and late remission was achieved in 21 patients (6.4%). 17 patients (5.2%) never achieved remission. 94.8% of the cohort experienced at least one remission, with first relapse, second relapse, and third relapse occurring in 115 patients (35.3%), 61 patients (18.7%), and 28 patients (8.6%), respectively. At the end of follow-up period, 281 patients (86.2%) were in terminal remission. 194 patients (59.6%) showed a continuous remitting course, and 87 patients (26.7 %) showed a remitting-relapse course. 45 patients (13.8%), including worsening courses in 28 patients (8.6%) and drug resistant courses in 17 patients (5.2%), did not show terminal remission. Markov process disclosed that children with epileptic encephalopathy and symptomatic partial epilepsy were less likely to show remission than children with idiopathic partial or generalized epilepsy (P<0.001).

Conclusion: Only 13.8% of children with new-onset epilepsy have poor seizure outcome in terms of never achieving remission or persistent seizure after achieving at least one remission. The etiology of epilepsy syndrome is an important factor determining seizure outcome.

Key Words : Seizure, Natural history, Relapse, Remission

Introduction

The natural history of epilepsy has been investigated and reported in treated cases as it is ethical to treat patients with proper antiepi-

접수 : 2012년 6월 8일, 수정 : 2012년 7월 12일
승인 : 2012년 7월 19일
책임저자: 김성환, 아주대학교 의과대학 소아과학교실
Tel: 031)219-5162, Fax: 031)219-5169
E-mail: pedkim@ajou.ac.kr

leptic drugs (AEDs) in current practice, except in underdeveloped countries and medically unprivileged areas. Therefore, the natural history of epilepsy usually refers to treated cases of epilepsy[1].

Seizure outcome in treated epilepsy has been simply described in terms of remission and relapse after remission at a certain moment after initiation of AED treatment[2, 3]. In one particular study, 47% of patients became seizure free with first-line AED and 14% became seizure free with a second or third drug[4]. It has led to conclude that patients unresponsive to initial AED are likely to have refractory epilepsy. Similar studies have shown that as many as 20-40% of newly treated patients with epilepsy will not enter remission and that such resistance may be fully developed even before the first seizure or treatment, or later in the course of epilepsy [2, 4-7]. However, early determination of intractability in treated epilepsy may overlook patients with possible late remission. In fact, repeated remissions and relapses may frequently occur over many years during the treatment course. It is challenging to exactly analyze and predict treatment outcome as different epilepsy syndromes have varying prognosis and their natural history are often much more dynamic than anticipated. In a study by Sillanpää et al.[8], different patterns of evolution of treated epilepsy is described in terms of early and late remission, remitting course, remitting-relapsing course, worsening course and drug resistance course. With such complex natural history, it is difficult to predict the long-term seizure outcome in new-onset childhood epilepsy. It is important to decide the likely clinical course of the childhood onset epilepsy after taking into account of individual result after a year of AED treatment and consider different prognosis of epileptic syndromes in each individual patient.

Therefore, we investigate the different evolution patterns of long-term seizure outcome in treated new-onset pediatric epilepsy and the types of epilepsy syndromes that influence long-term seizure outcome in Korean children.

Materials and Methods

1. Patients and Study Design

The study population included 326 children with new-onset epilepsy who were living in the catchment area of Pediatric Epilepsy Clinic of Ajou University Medical Center from January 1999 to December 2004. Ajou University Medical Center is a tertiary referral center covering southern half of the Gyeonggi Province of Korea. Eligible patients were aged from 2 months to 15 years at the time of diagnosis of new-onset epilepsy. In this study, history taking and general physical/neurological examination were performed by pediatric neurologists. Electroencephalography (EEG) of the enrolled patients was recorded at Clinical Neurophysiology Laboratory of Ajou University Medical Center, and had been interpreted by one pediatric epileptologist. The etiology of seizures was documented by patient history, neurological examination, and brain magnetic resonance imaging (MRI). From the information available at the time of initial diagnosis, we diagnosed and classified the disease of each patient into epilepsy or a specific epilepsy syndrome. As we were interested in long-term seizure outcome, we used the classification of epilepsy as reported at the time of initial diagnosis of epilepsy[9-12]. We also classified epilepsy or epilepsy syndrome into five

groups according to the type of epileptic seizures, EEG findings, etiology of seizures, and concept of specific epilepsy syndromes: Idiopathic generalized, Idiopathic partial, Cryptogenic partial, Symptomatic partial, and Epileptic encephalopathy. From the time of diagnosis, monotherapy was started according to the recommended therapeutic guideline[9] in all cases. When initial monotherapy failed, another AED was given as an alternative monotherapy or adjunctive therapy based on therapeutic guidelines. Patients were regularly seen in an out-patient clinic by the same pediatric epileptologist every 2-3 months, or earlier if clinically indicated. For each patient, seizure outcome to each AED were recorded on case-record forms in terms of remission of seizure or recurrence after initial remission of seizure, with limit of up to three remission periods with relapses. A long-term prospective follow-up from the period of enrollment to November 2009 was conducted to examine the evolution pattern and role of epilepsy syndrome on seizure outcome in terms of remission and relapse over the entire follow-up period.

2. Definition of Etiology of seizure, Epilepsy syndrome, Remission, and Relapse

Epileptic seizures, epilepsies, epilepsy syndromes, epileptic encephalopathy, and etiology of seizures were defined according to the guidelines of the International League Against Epilepsy[10-13]. Remission of epilepsy was defined as a seizure free period of 5 or more consecutive years with or without antiepileptic treatment[14]. Terminal remission was defined as sustained seizure free state for more than 1 year at the end of follow-up. Remission of seizure was defined as a 1 year seizure free state after initiation of treatment, achieved either early, within 12 months after initial AED treatment, or late, after more than 1 year of initial AED treatment. Relapse was defined as the occurrence of repeated seizures after a patient had attained a 1 year seizure free state. However, a single seizure occurring immediately after drug withdrawal, poor compliance, or intercurrent infection was not classified as a relapse. Should terminal remission be uninterrupted from the start of treatment to the end of follow-up, it was defined as a remitting course. When interrupted by relapse, it was defined as a remitting-relapsing course. Should remission be followed by relapse without further terminal remission, it was defined as a worsening course. Remission not achieved during follow-up despite adequate treatment was defined as a drug-resistant course. Four different patterns of seizure outcomes were anticipated.

3. Statistical analysis

The probability of repeated remission and relapse from the initial diagnosis of epilepsy, up to three different remission episodes per patient, were examined with Markov process. This study focused on the evolution pattern of seizure outcome in the overall cohort as well as by epilepsy syndrome group. Comparison of seizure outcomes between the five different epilepsy syndrome groups were analyzed by Chi-square test. A p-value of <0.05 was considered statistically significant.

Results

1. Demographic features

326 children with new-onset epilepsy were recruited into this cohort study in a single center. Study cohort included 168 boys and

158 girls. Their mean age at initial diagnosis of new-onset epilepsy was 7.2±3.8 years (range: 2 months-15 years of age). The mean follow-up at the time of analysis was 79.3±25 months (range: 23-131 months).

2. Long-term seizure outcome: remission and relapse

309 of 326 patients (94.8%) experienced an initial remission after initiation of AED treatment. However, 17 of 326 patients (5.2%) did not enter remission from the start to the end of follow-up. Relapse occurred in 115 of 309 patients (37.2%) who attained initial remission with AED treatment. At the end of follow-up, 281 of 326 patients (86.2%) were in terminal remission with or without antiepileptic drugs. However, 45 patients (13.8%) were not in terminal remission or never experienced remission. Early remission occurred in 288 patients (88.4%). In 182 (55.9%) of them, initial remission continued, uninterrupted by relapse to terminal remission. Late remission was achieved in 21 of 326 patients (6.4%), and 12 of them (3.7%) achieved terminal remission without any relapse. Therefore, terminal remission uninterrupted by relapse, defined as a remitting course, was found in a total 194 of 326 patients (59.6%). In 115 of 326 patients (35.2%), remission was followed by one or more relapse; first relapse in 115 patients, 2nd relapse in 61, and 3rd relapse in 28 patients. Following a relapse after early or late remission, 87 patients (26.6%) achieved terminal remission (remitting-relapsing course), but 28 patients (8.6%) did not enter terminal remission (worsening course of epilepsy). 17 of 326 patients (5.2%) did not enter remission from the start to the end of follow-up (drug resistant course) (Fig. 1).

3. Seizure outcome according to the type of epilepsy

Of 326 children with new-onset epilepsy in this single center based cohort study, 48 patients (14.7%) had idiopathic generalized epilepsy, 101

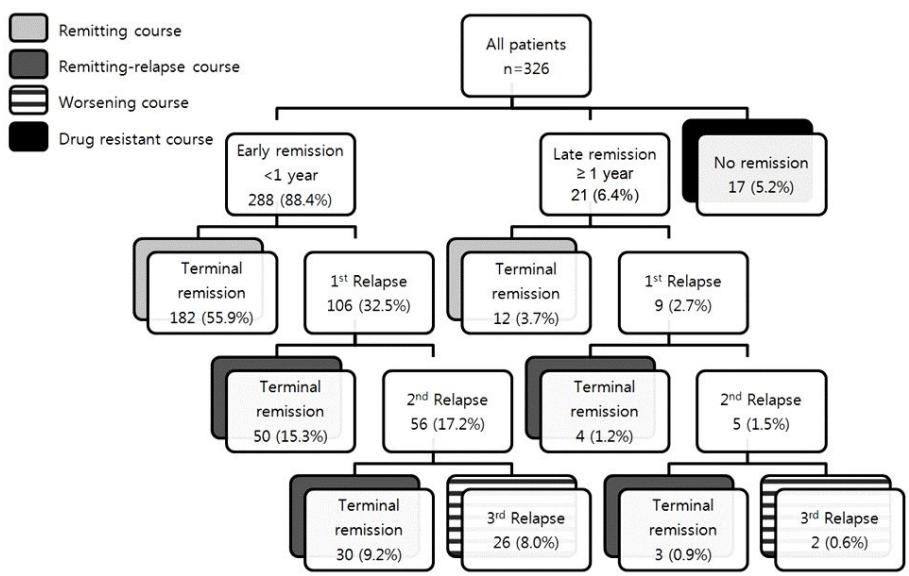

Fig. 1. 326 pediatric patients with new-onset epilepsy and their seizure outcome.

(31%) idiopathic partial, 117 (35.9%) cryptogenic partial, 48 (14.7%) symptomatic partial, and 12 (3.7%) epileptic encephalopathy. In 48 patients with idiopathic generalized epilepsy, 40 patients (83.3%) showed remitting course of epilepsy, 6 patients (12.5%) remitting-relapsing course, and 2 patients (4.2%) worsening course. Among 101 patients with idiopathic partial epilepsy, 83 patients (82.2%) showed remitting course; 17 patients (16.8%) remitting-relapsing course and 1 patient (1.0%) drug resistant course. Among 117 patients with cryptogenic partial epilepsy, 50 patients (42.7%) showed remitting course, 48 patients (41.0%) remitting-relapsing course, 14 patients (12.0%) worsening course and 5 patients (4.3%) drug resistant course. However, in 48 patients with symptomatic partial epilepsy, remitting course were shown in 16 patients (33.3%), remitting-relapsing course in 15 patients (31.3%), worsening course in 10 patients (20.8%), and drug resistant course in 7 patients (14.6%). In 12 patients with epileptic encephalopathy, 5 patients (41.7%) showed remitting course, 1 patient (8.3%) remitting-relapsing course, 2 patients (16.7%) worsening course, and 4 patients (33.3%) drug resistant course of epilepsy (Table 1). In terms of seizure outcome by the type of epilepsy, percentage of patients in remitting course and remitting-relapsing course are significantly higher

Table 1. Seizure Outcome of New-onset Pediatric Epilepsy according to the Type of Epilepsy

Etiology of epilepsy		Remitting course	Remitting-relapsing course	Worsening course	Drug resistant	Total
Idiopathic generalized epilepsy	Count	40	6	2	0	48
	%within Etiology of epilepsy	83.3	12.5	4.2	0.0	100.0
	%within natural history	20.6	6.9	7.1	0.0	14.7
	%of Total	12.3	1.8	0.6	0.0	14.7
Idiopathic partial epilepsy	Count	83	17	0	1	101
	%within Etiology of epilepsy	82.2	16.8	0.0	1.0	100.0
	%within natural history	42.8	19.5	0.0	5.9	31.0
	%of Total	25.5	5.2	0.0	0.3	31.0
Cryptogenic partial epilepsy	Count	50	48	14	5	117
	%within Etiology of epilepsy	42.7	41.0	12.0	4.3	100.0
	%within natural history	25.8	55.2	50.0	29.4	35.9
	%of Total	15.3	14.7	4.3	1.5	35.9
Symptomatic partial epilepsy	Count	16	15	10	7	48
	%within Etiology of epilepsy	33.3	31.3	20.8	14.6	100.0
	%within natural history	8.2	17.2	35.7	41.2	14.7
	%of Total	4.9	4.6	3.1	2.1	14.7
Epileptic encephalopathy	Count	5	1	2	4	12
	%within Etiology of epilepsy	41.7	8.3	16.7	33.3	100.0
	%within natural history	2.6	1.1	7.1	23.5	3.7
	%of Total	1.5	0.3	0.6	1.2	3.7
Total	Count	194	87	28	17	326
	%within Etiology of epilepsy	59.5	26.7	8.6	5.2	100.0
	%within natural history	100.0	100.0	100.0	100.0	100.0
	%of Total	59.5	26.7	8.6	5.2	100.0

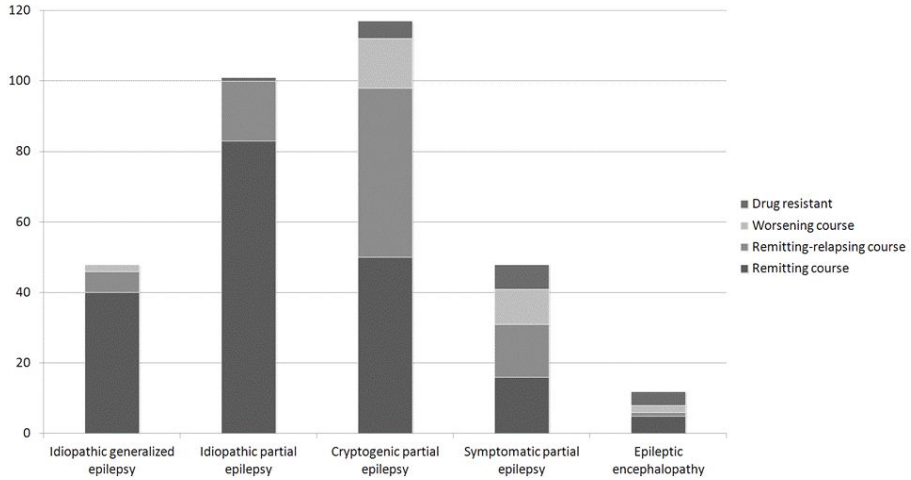

Fig. 2. Number of patients presenting different seizure outcome in each group.

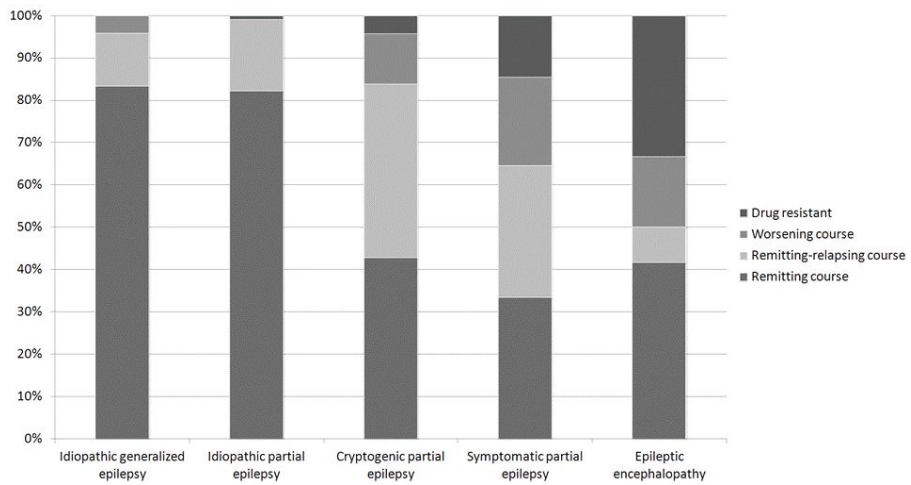

Fig. 3. Proportion of different seizure outcomes in each etiologic group of epilepsy. Percentage of patients in remitting course and remitting-relapsing course is significantly higher in idiopathic partial and idiopathic generalized epilepsy than those in symptomatic partial and epileptic encephalopathy ($P<0.001$).

in idiopathic partial and idiopathic generalized epilepsy than those in symptomatic partial and epileptic encephalopathy, $P<0.001$ (Table 1, Fig. 2, Fig. 3).

Discussion

Many studies have shown that as many as two of three newly treated patients with epilepsy enter long-term remission for several years with the first AED[2, 5, 15]. The remaining third of patients have drug-resistant epilepsy. However, treated new-onset epilepsy of 326 children in our study showed quite favorable results with 309 patients (94.8%) having at least one remission during the follow-up period and 281 (86.2

%) patients in terminal remission at the end of follow-up. 194 patients (59.6%) achieved continuous seizure free state uninterrupted by seizure recurrence from initiation of AED treatment. Only 45 patients (13.8%) were not in terminal remission at the end of the follow-up, including 17 patients (5.2%) who never achieved remission from initiation of AED treatment. This result is somewhat more preferable than those of study by Sillanpaa et al.[8] where 81% of patients achieved at least one remission and 19% of patients never achieved remission. These favorable results can be explained by three different aspects. First, the percentage of idiopathic epilepsies is higher in our study than those of the study by Sillanpaa et al.[8] (45.7% versus 31.2%). It is well known that idiopathic epilepsies have better response to first-line AED than symptomatic or cryptogenic epilepsies [16]. Second, while valproic acid was not initially available in the study by Sillanpää et al.[8], it was usually used as the first-line AED in our study. Valproic acid has a broad spectrum antiepileptic activity and shown to control seizure more effectively than other first-line AEDs[16]. Third, various newly developed AEDs were available and used in patients where the first or second AED had failed to control seizure. It may have contributed to better seizure outcome in our study.

In our study, seizure evolution pattern was complicated and extremely variable as expected, showing repeated events entering remissions and relapses from remission. 288 patients (88.4 %) achieved early remission in the first year after initiation of AED treatment. Early remission was sustained without relapse and ended in terminal remission in 182 of them (55.9%). However, 106 patients (32.5%) experienced seizure relapses more than once despite having achieved early remission. 26 patients (8.0%) had several relapses and did not enter terminal remission at the end of follow-up. On the other hand, 21 patients (6.4%) gained late remission only after more than 12 months of AED treatment. 12 patients of them had sustained seizure remission uninterrupted by relapse and entered terminal remission at the end of follow-up despite late remission. There was a distinct group of patients (17 patients, 5.2%) who never achieved a remission from initiation of AED treatment to the end of follow-up. These results reconfirm the dynamic and complicated natural history of treated new-onset epilepsy in Korean children. Many studies have tried to evaluate remission rates after unsuccessful initial AED treatment. Camfield et al.[17] found that 42% of 72 children that had failed to respond to first AED achieved late remission. Sillanpää et al.[8] found that 50% of adults with childhood onset epilepsy achieved late remission. In a cohort study by Luciano et al.[18], 28% of 155 patients with uncontrolled chronic epilepsy eventually entered remission during follow up. On the basis of our study results and the results of several authors mentioned above, we insist that failure to enter early remission with initial AED treatment does not always predict long-term drug resistance or poor outcome in every case, and also that it may not be an absolute indicator for predicting long term failure. In addition, these results oppose the opinion by Kwan et al.[4] that refractory epilepsy can be easily identified by initial treatment response and that early surgical intervention is recommend if there is failure of seizure control with first and second AED treatment. True drug resistance or remission failure

can only be determined after a long-term follow up.

Etiology of epilepsy is an important factor predicting seizure outcome in pediatric epilepsy. Several studies have confirmed poor seizure outcome in pediatric epilepsy of symptomatic etiology[19-23]. Sillanpää et al.[24] reported higher terminal remission rates in idiopathic or cryptogenic epilepsy than symptomatic epilepsies. They also compared seizure free rate and chance of intractable epilepsy between patients with cryptogenic etiology and symptomatic etiology. Intractable epilepsy was significantly higher in symptomatic epilepsy than cryptogenic etiology (40% versus 7%). Terminal seizure free rate was also lower in symptomatic than in cryptogenic etiology (55% versus 81%). In our study, percentages of patients in remitting course and remitting-relapsing course are significantly higher in idiopathic partial and idiopathic generalized epilepsy than symptomatic partial and epileptic encephalopathy ($p<0.001$). The result of our study was quite similar to those of the study by Sillanpää et al[24]. Pediatric cohorts are different compared to adult cohorts in that the proportion of idiopathic epilepsies are higher in children and that idiopathic epilepsies include benign epilepsy with centrotemporal spikes, Panayiotopolous syndrome and benign infantile epilepsies, which have known favorable prognosis. On the other hand symptomatic epilepsies include neurologic deficits such as intrauterine insults, malformation of cortical development, genetic encephalopathies, which are presumed to be present from birth. It may be very difficult to achieve remission in this group regardless of treatment[25].

In conclusion, the natural history of new-onset treated epilepsy in Korean children is very complex and dynamic as remission and relapse is capable of repeating several times throughout the entire course of epilepsy during AED treatment. Only 13.8% of children with new-onset treated epilepsy have poor outcome in terms of never achieving remission or persistent seizure relapse after achieving early or late remission. The type of epilepsy syndrome is an important factor determining long-term seizure evolution pattern.

However, our study has several limitations in terms of study population and epidemiologic definition of seizure remission. This study was done in a single center and was not a population based study. Definition of seizure remission in this study, which was defined as a 1 year seizure free rate, may be too short as true remission can only be defined after a life-long follow-up. Therefore, extensive follow-up in a population based study is needed to overcome these limitations.

한 글 요 약

새로 진단된 소아 간질 환자의 자연사: 단일기관의 장기 추적관찰 코호트 연구

아주대학교 의과대학 소아과학교실,
*임상역학 및 생물통계실**

신원섭 · 최일락 · 장유진
이현영* · 신승수 · 김성환

목 적: 간질의 경과는 관해와 재발이 반복적으로 발생할 수 있다는 관점에서 볼 때 매우 복잡하고 다양한 경과를 보인다. 저자는 새로 진단된 소아 간질 환자에서 항경련제 치료 후 나타날 수 있는 간질의 자연사에 대한 다양한 양상을 조사하고 간질 증후군의 유형에 따른 경과를 알아보려 한다.

방 법: 새로 진단된 15세 이하 소아 간질 환자 326명을 대상으로 항경련제 치료 후 관해와 재발 양

상을 장기간 추적 관찰하여 간질의 자연사를 조사하였다. 대상환자에서 나타나는 다양한 형태의 관해와 재발 양상과 간질증후군에 따른 관해와 재발 양상의 특성을 조사하였다. 반복적으로 발생하는 관해와 재발 확률은 Markov process로 분석하였다.

결 과: 평균 79±27개월간 추적 관찰한 326명의 소아 간질 환자 중 288명(88.4%)은 항경련제 치료 시작 후 첫 해에 조기 관해를 보였으나, 21명(6.4%)은 치료 시작 1년 후 지연 관해를 보였다. 그러나 17명(5.2%)은 처음부터 관해가 오지 않았다. 치료 시작 후 관해를 보인 309명(94.8%)의 환자들에서 첫 재발이 115명(35.3%), 두번째 재발이 61명(18.7%), 세번째 재발이 28명(8.6%)에서 발생하였으며, 추적 관찰 종결시 281명(86.2%)에서 최종 관해 상태를 보였다. 전체 환자 326명 중 194명(59.6%)은 처음 관해 후 지속적으로 관해가 유지되는 경과를 보였고, 87명(26.7%)은 관해와 재발이 반복되는 경과를 보였으며, 28명(8.6%)은 더 이상 관해를 보이지 않고 악화되는 경과를 보였다. 악화되는 경과를 보이는 28명과 항경련제에 전혀 반응을 보이지 않는 17명(5.2 %)을 포함한 45명(13.8%)의 환자가 최종 관해를 이루지 못하였다. Markov process 검증에서 간질성 뇌증과 증후성 부분간질 환자군이 특발성 부분간질과 전신성 간질 환자군에 비해 관해 확률이 낮았다(P<0.001).

결 론: 새로 진단된 소아 간질 환자의 13.8%의 환자에서 지속적으로 관해가 오지 않거나 초기에 관해가 오더라도 이후 지속적으로 재발을 보이는 불량한 예후를 보였다. 소아 간질에서 간질 증후군의 유형은 간질의 자연사를 결정하는 중요한 인자로 작용한다.

References

1) Forsgren L, Hesdorffer D. Epidemiology and Prognosis of Epilepsy. In: Shorvon SD, Perucca E, Engel J, editors. The Treatment of Epilepsy. 3rd ed. Wiley-Balckwell, 2009:21-31.
2) Annegers JF, Hauser WS, Elveback LR. Remission of seizures and relapse in patients with epilepsy. Epilepsia 1979;20:729-37.
3) Camfield C, Camfield P, Gordon K, Dooley J. Does the number of seizures before treatment influence ease of control or remission of childhood epilepsy? Not if the number is 10 or less. Neurology 1996;46:41-4.
4) Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314-9.
5) Cockerell OC, Johnson AL, Sander JW, Hart YM, Shorvon SD. Remission of epilepsy: results from the National General Practice Study of Epilepsy. Lancet 2006;367:1087-100.
6) Berg AT, Langfitt J, Shinnar S, Vickrey BG, Sperling MR, Walczak T et al. How long does it take for partial epilepsy to become intractable? Neurology 2003;60:186-90.
7) Goodridge DM, Shorvon SD. Epileptic seizures in a population of 6000. II: Treatment and prognosis. Br Med J (Clin Res Ed) 1983;287:645-7.
8) Sillanpää M, Schmidt D. Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. Brain 2006;129:617-24.
9) Wheless JW, Clarke DF, Arzimanoglou A, Carpenter D. Treatment of pediatric epilepsy: European expert opinion, 2007. Epileptic Disord 2007;9:353-412.
10) Commission on Classification and Terminology of the International League Against Epilepsy, Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22:489-501.
11) Commission on Classification and Terminology of the International League Against Epilepsy, Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389-99.
12) Commission on Epidemiology and Prognosis, International League Against Epilepsy, Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993;34:592-6.
13) Engel J Jr, International League Against Epilepsy, A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. Epilepsia 2001;42:796-803.
14) Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with

epilepsy. Epilepsia 1979;20:729-37.
15) Camfield P, Camfield C. Childhood epilepsy: what is the evidence for what we think and what we do? Child Neurol 2003;18:272-87.
16) Ma MS, Ding YX, Ying W, Fang F, Ding CH, Zou LP. Effectiveness of the first antiepileptic drug in the treatment of pediatric epilepsy. Pedatr Neurol 2009;41:22-6.
17) Camfield PR, Camfield CS, Gordon K, Dooley JM. If a first antiepileptic drug fails to control a child's epilepsy, what are the chances of success with the next drug? J Pediatr 1997;131:821-24.
18) Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. Ann Neurol 2007;62:375-81.
19) Berg AT, Lin J, Ebrahimi N, Testa FM, Levy SR, Shinnar S. Modeling remission and relapse in pediatric epilepsy: application of a Markov process. Epilepsy Res 2004;60:31-40.
20) Berg AT, Levy SR, Novotny EJ, Shinnar S. Predictors of intractable epilepsy in childhood: a case-control study. Epilepsia 1996;37:24-30.
21) Bertol V, Oliveros A, Gros MB, Brieva L. Prognostic value of data from clinical, EEG and neuroimaging assessment in epilepsy with complex partial seizures. Rev Neurol 1996;24:964-8.
22) Ko TS, Holmes GL. EEG and clinical predictors of medically intractable childhood epilepsy. Clin Neurophysiol 1999;110:1245-51.
23) Trinka E, Martin F, Leuf G, Unterberger I, Bauer G. Chronic epilepsy with complex partial seizures is not always medically intractable-a long-term observational study. Acta Neurol Scand 2001;103:219-25.
24) Sillanpää M, Schmidt D. Early seizure and aetiology predict long-term medical outcome in childhood-onset epilepsy. Brain 2009;132:989-98.
25) Berg AT, Testa FM, Levy SR. Complete remission in nonsyndromic childhood-onset epilepsy. Ann Neurol 2011;70:566-73.