Remission and Long-Term Prognosis of Epilepsy from Current Epidemiological Evidences

김 명 규
전남대학교 의과대학 신경과

Myeong-Kyu Kim
Department of Neurology, Chonnam National University Medical School

Complete remission of seizures off medication is an ultimate goal in epilepsy care. Fifty-eight percent of children with newly diagnosed nonsyndromic epilepsy on monotherapy achieved 5 years seizure- and medication-free. In adults with a newly diagnosed unprovoked epileptic seizure, cumulative 1-, 3- and 5-year remission rates, calculated from the date of epilepsy diagnosis were 68%, 64%, and 58%, respectively in a condition not allowing polytherapy more than 2 AEDs. These data suggest that seizure prognosis for the majority of patients with newly diagnosed epilepsy is good, regardless of age of the patients with epilepsy. However, no evidence was available yet for relapse rate after being seizure-free for 10 years and for the details of what number of seizure-free years off medication should be required for achieving remission in adults with epilepsy. Long-term prognosis of epilepsy depends on various factors affecting relapse risk of seizure, among which the optimal timing and mode of AED withdrawal are two important questions that physicians are being faced with. The cumulating evidence tend to support later withdrawal (seizure free > 2 years) in children and slower withdrawal in adult. However, the available literature to date does not allow for an algorithmic approach to achieve complete remission or a better long-term prognosis of epilepsy. Therefore, physician should take into account all factors predictive of seizure recurrence, the medical, legal, and social consequences of drug withdrawal and subsequently discuss this information with the patient or his or her caregivers.

Key Words: Long-term prognosis; Epilepsy

Introduction

Epilepsy is not a lifelong disorder in all patients and complete remission of seizures off medication is an ultimate goal in epilepsy care. Although recent hospital- and population-based studies have suggested a good prognosis,[1] there are considerable differences among these studies regarding definitions of remission, duration of follow-up, and whether the study population consists of patients with single or recurrent seizures. Even the conventional definition of epilepsy does not allow a patient to outgrow epilepsy. In 2005, a Task Force of the International League Against Epilepsy (ILAE) formulated conceptual (can be translated for specific purpose into operational or practical) definitions of epilepsy for purposes of clinical diagnosis and, in December of 2013, the ILAE Executive Committee adopted the recommendations as a position of the ILAE. According to the operational (practical) definitions,[2] epilepsy is considered to be "resolved" (the Task Force used the term "resolved" instead of "remission" or "cure" with accountable reasons) for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years. However, delineation of circumstances in which a better long-term prognosis of epilepsy would be achieved is often based on inconclusive data.

Here, recent epidemiologic studies regarding remission and long-term prognosis of epilepsy will be reviewed.

Myeong-Kyu Kim
Department of Neurology, Chonnam National University Medical School, Gwangju, Korea
TEL: +82-62-220-6161 FAX: +82-62-228-3461
E-mail: mkkim@jnu.ac.kr

Remission of Epilepsy

1. Review of Longitudinal Cohort Study of The Prognosis of Epilepsy in Last Several Decades

Shorvon et al. (2013)[1] reviewed more than 20 cohort studies regarding the prognosis of epilepsy conducted since the late 1970s and concluded that (i) epilepsy has an often good prognosis with 65-85% of cases eventually entering long-term remission, and an even higher proportion of cases entering a short-term remission; (ii) the likelihood of long-term remission of seizures is much better in newly diagnosed cases than in patients with chronic epilepsy; (iii) the early response to treatment is a good guide to longer term prognosis (although not inevitably so, as in a minority of cases seizure remission can develop after prolonged activity); (iv) the longer is the remission (and follow-up), the less likely is subsequent recurrence; (v) the longer an epilepsy is active, the poorer is the longer term outlook; (vi) delaying treatment, even for many years, does not worsen long-term prognosis. Although these epidemiologically-valid cohort studies have an important role in contributing to an understanding, at least in part, of natural history of epilepsy, there are considerable differences among these studies regarding inclusion criteria including seizure types, age of seizure onset or etiology of epilepsy, definitions of remission, duration of follow-up, and whether the study population consists of patients with single or recurrent seizures.

2. Representative Cohort Study Regarding Remission of Epilepsy in Child or Adult

In a prospective community-based cohort study (2011)[3] in which children with nonsyndromic epilepsy on monotherapy over the course of ≥10 years from initial diagnosis were included and complete remission was defined arbitrarily as 5 years seizure- and medication-free, 170 of the 294 children (58%) who met the inclusion criteria achieved complete remission. The probability of achieving complete remission by 5, 8, 10, and 15 years after diagnosis of epilepsy was 3%, 31%, 46%, and 60%. Among them achieved complete remission, 10 (6%) relapsed. Relapses occurred 0.4 to 7.5 years after the date of attaining complete remission; the probability of relapse at 1, 5, and 8 years after complete remission was 1%, 5%, and 8%.

In a population-based adult (more than 17 years old) cohort study (2001)[4] in which the probability of achieving remission of seizures after a newly diagnosed unprovoked epileptic seizure was investigated, cumulative 1-, 3- and 5-year remission rates, calculated from the date of epilepsy diagnosis were 68%, 64%, and 58%, respectively in a condition not allowing polytherapy more than 2 AEDs. The time required after epilepsy diagnosis to achieve a 1-year remission of seizures does not affect the probability of additionally achieving a 5-year remission, which means that achieving a 1-year remission implies equal probabilities also to achieve a 5-year remission, irrespective of when the 1-year remission is achieved.

Taken together, seizure prognosis for the majority of patients with newly diagnosed epilepsy is good, regardless of age of the patients with epilepsy. However, no evidence was available yet for relapse rate after being seizure-free off medication for 10 years and for the details of what number of seizure-free years off medication should be required for achieving remission in adults with epilepsy.

Long-term Prognosis of Epilepsy

Long-term prognosis of epilepsy depends on the type of epilepsy, age, syndrome, etiology, treatment, and many other factors including EEG abnormality or seizure-free period before AED discontinuation, among which, especially, the optimal timing and mode of AED withdrawal are two important questions that physicians are being faced with.

1. Optimal Timing of AEDs Withdrawal; Early or Late?

Because prolonged usage of AEDs may have long-term side effects and may potentially affect the prognosis or quality of life, it is logical to attempt to discontinue the medication when a person with epilepsy is in remission (free of seizures for some time). The physician contemplating withdrawal of AEDs is faced with two important questions:

timing of withdrawal and mode of withdrawal. However, the decision to discontinue AEDs is often based on inconclusive data.

An American Academy of Neurology task force drafted guidelines regarding optimal timing of AED discontinuation as a range between 2 to 5 seizure free years (AAN 1994)[5] and a large, randomized population-based study conducted prospectively in the UK required all individuals to be seizure free for at least 2 years (MRC 1991).[6] But the required duration of seizure free before discontinuing AEDs was chosen arbitrarily.

In a review by Cochrane Epilepsy Group[7] in which seven eligible controlled trials (924 randomized children) were included, there is evidence that discontinuing medications prior to at least two seizure free years is associated with a higher recurrence risk than waiting for two or more seizure free years in children, particularly if individuals have an abnormal EEG and partial seizures. However, the optimal time of withdrawal is not clear because two years was chosen arbitrarily. Furthermore, the review could not provide sufficient evidence to establish when to withdraw AEDs in children with generalized seizures and in adults with seizure free. The most commonly reported rate of relapse after 2 years of seizure freedom in children with cryptic focal epilepsy is approximately 30 to 40%.[8] In a small-sized retrospective study[9] in which 59 patients with idiopathic generalized epilepsy (IGE) were included, the overall relapse rate was 52% after at least 2 years of seizure freedom and depends on the diagnosis of specific IGE syndrome; the lowest was in CAE, the highest in JME. Taken together, the cumulating evidence tend to support later AEDs withdrawal (seizure free 〉2 years) in children.

Only few studies were concern with the optimal timing of AED withdrawal for adult. A randomized controlled study for adults with focal epilepsy having more than 2 years of seizure freedom on AED monotherapy,[10] reported that seizure relapse at 12 months occurred in 15% of the withdrawal group and 7% of the nonwithdrawal group (RR 2.46; 95% CI: 0.85-7.08; p=0.095) and the overall relapse rate was 27% after a median of 41 months off medication. In a prospective nonrandomized study[11] in which 49 adult patients with mainly focal epilepsy were included, the overall relapse rate was 57% after 4 years of seizure freedom. Contrary to these data that showed no correlation between risk of seizure relapse and seizure-free period before discontinuing AEDs, a definite linear correlation between relapse and number of years of remission while on treatment was noted in a prospective nonrandomized study[12] in which 87.3% of all participants were adults with epilepsy. After adjusting for the principal prognostic factors, the risk of seizure relapse was 2.6 times (in patients with 2 years of remission) and 1.6 times (in patients with 3 to 5 years of remission) that of patients with more than 5 years of remission at study entry (p=0.001). Although these data also provide evidence that at least 2 seizure free years are required before discontinuing AED and longer seizure free years before discontinuing AED may lower the rate of relapse, the optimal time of withdrawal in adults remain to be clear.

2. Mode of AEDs Withdrawal; Rapid or Slow?

Risk of seizure relapse due to rapidity of AEDs discontinuation is not well defined as very few studies were concerned with the topic.

In 1999, Altunbasak et al.[13] reported that the relapse rate for the children whose medication was withdrawn gradually over 2 to 5 months was 38.9%, whereas it was 16.5% for the children whose drug was withdrawn over more than 5 months (p〈0.05). However, in a review by Cochrane Epilepsy Group[14] in which only 1 randomized controlled trial with weak methodology was included and the authors tired to quantify the risk of seizure recurrence after rapid (taper period of 6 weeks) or slow (taper period of 9 months) discontinuation of antiepileptic drugs in 149 children with epilepsy who are in remission, they could not derive any reliable conclusions regarding the optimal rate of tapering of AEDs because of methodological deficiencies and small sample size.

The corresponding topic in adults with epilepsy was issued in a relatively small-sized retrospective study[15]

where relapse rate in patients with taper period over 12 months decreased to 63% of that in patients with taper period under 6 months (p=0.037). However, in a prospective study[16] analyzed the seizure outcome after AEDs discontinuation of 310 consecutive patients who underwent anterior temporal lobectomy, there was no significant difference in the taper period between seizure recurrence group and seizure-free group (45.41±16.77 and 44.19± 20.64 months respectively). These data are in favor of slow withdrawal, even though the taper period has come down arbitrarily to 3 to 6 months in some recent studies.[14]

To summarize, in view of lack of well-controlled studies, there is no consensus on the mode of withdrawal.

Conclusion

Seizure prognosis for the majority of patients with newly diagnosed epilepsy is good, regardless of age of the patients with epilepsy and the cumulating evidence tend to support later withdrawal (seizure free 〉 2 years) in children and slower withdrawal in adult to achieve a better long-term prognosis. However, the available literature does not allow for an algorithmic approach to AED discontinuation. Therefore, physician should take into account all factors predictive of seizure recurrence, the medical, legal, and social consequences of drug withdrawal and subsequently discuss this information with the patient or his or her caregivers.

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