

Chapter 11

Termination of Epilepsy Treatment

CQ 11-1

How many years after seizure remission should treatment termination be considered?

Summary

In children, consider treatment termination after seizures have remitted for at least 2 years.

In adults, more cautious consideration should be given, but in the case of a desire of child-bearing, actively consider dose reduction and termination.

Comment

Termination of epilepsy treatment is one of the most difficult clinical decisions. Although much evidence has been accumulated, there is no clear consensus on the timing of treatment termination.

In children, some epilepsy syndromes have good prognosis (= idiopathic partial epilepsy). To avoid adverse effects of long-term treatment with antiepileptic drugs on cognitive and behavioral development, the benefits of treatment termination are great. In adults, such subgroup with good prognosis has not been reported, and the risk of seizure recurrence by drug termination is higher than in the case of childhood-onset epilepsy¹⁾. Because social factors such as employment and driving license have great impact on the decision in adults, more careful consideration is required. In women whose seizures are in remission, a desire of child-bearing is a good opportunity to consider treatment termination. If seizure recurs in the process of treatment withdrawal, the seizure is controlled by restarting therapy in most cases, although the seizure control may be difficult in some patients²⁾. We should make a final decision on treatment termination individually by comprehensively considering various conditions of each patient (in particular, the presence or absence of a poor prognostic factor) together with respect for the intentions of the patients and their families.

As for the timing of treatment termination in children, there is a Cochrane review that compared an early treatment withdrawal group (seizure remission for less than 2 years) and a late treatment withdrawal group (seizure remission for more than 2 years)³⁾. In this analysis, the early treatment withdrawal group had a higher risk of seizure relapse than the late treatment withdrawal group, with a relative risk of 1.32 (1.02–1.70). Particularly, in patients with partial seizure or EEG abnormality, the risk of relapse was even higher; the relative risk of early withdrawal was 1.52 (0.95–2.41), and that of late withdrawal was 1.67 (0.95–3.00). There is no reliable evidence on generalized seizures. In children, there is little risk of relapse if treatment is terminated after 2 years or longer of seizure remission.

In adults, there is no evidence that compares early and late treatment termination. According to the results of a randomized controlled trial of 1,013 adult epilepsy patients who had seizure remission for more than 2 years, the complete remission rate was 78% in the patients who continued treatment, and 59% in those who withdrew treatment after 2 years of follow-up⁴⁾. The most important factor influencing seizure relapse was the duration of seizure remission.

■ References

- 1) Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. *Neurology*. 1994; 44(4): 601-608.
- 2) Schmidt D, Löscher W. Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. *Acta Neurol Scand*. 2005; 111(5): 291-300.
- 3) Sirven J, Sperling MR, Wingerchuk DM. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. *Cochrane Database Syst Rev*. 2015; (2): CD001902.
- 4) Medical Research Council Antiepileptic Drug Withdrawal Study Group. Randomised study of antiepileptic drug withdrawal in patients in remission. *Lancet*. 1991; 337(8751): 1175-1180.

■ Search formula and secondary reference sources

PubMed search: December 13, 2015

((“epilepsy” [MeSH Terms] OR “epilepsy” [All Fields]) AND (“therapy” [Subheading] OR “therapy” [All Fields] OR “therapeutics” [MeSH Terms] OR “therapeutics” [All Fields])) AND termination [All Fields] = 383. Finally the above references were included.

Does the risk of seizure recurrence differ depending on seizure type, epilepsy type, or epilepsy syndrome?

Summary

The risk of seizure recurrence differs depending on epilepsy syndrome.

Comment

According to a prospective study on treatment termination in 264 children with epilepsy by Shinnar et al.¹⁾, seizures recurred in 95 children (36%) during the follow-up period (average 58 months). In this study, among the epilepsy syndromes, no recurrences occurred in 14 children with idiopathic partial epilepsy (benign childhood epilepsy with centrotemporal spikes, benign Roland epilepsy), while seizures recurred in all 4 children with juvenile myoclonic epilepsy (JME)²⁾. Meanwhile, in a long-term follow-up (median 44.6 years) study of 66 patients with JME, 39 patients (59.1% of all patients) remained seizure-free for over 5 years (22.9 ± 10.9 years), 11 of whom (16.7% of all patients) had no antiepileptic drugs for over 5 years³⁾. Thus, the results are inconsistent among reports.

The above findings suggest that the diagnosis of epilepsy syndrome is critical when considering termination of treatment. However, there are few epilepsy syndromes in which a definite prognosis can be predicted. For the other epilepsy syndromes, the risk of seizure relapse is relative, and evidence is poor. In addition, many patients cannot be classified under one specific epilepsy syndrome. At least, the recurrence rate is higher in symptomatic epilepsy than in idiopathic epilepsy [relative risk 1.81 (1.21–2.70)]¹⁾.

There is not enough evidence on the risk of seizure recurrence for each of the seizure types. According to a study from Japan that analyzed the recurrence and clinical features of 556 patients with childhood-onset epilepsy who discontinued antiepileptic drug therapy, 80 patients (14.4%) had recurrence, and the rate was especially high in those who stopped drugs after adolescence²⁾. By epilepsy type, the rates were high in adolescent- or adult-onset idiopathic generalized epilepsy (31.3%), symptomatic localization-related epilepsy (25.2%), and cryptogenic or symptomatic generalized epilepsy (19.2%).

■ References

- 1) Shinnar S, Berg AT, Moshé SL, et al. Discontinuing antiepileptic drugs in children with epilepsy: a prospective study. *Ann Neurol*. 1994; 35(5): 534-545.
- 2) Yamatani M, Konishi T, Matsuzawa J, et al. Relapse of seizure after withdrawal of antiepileptic drug treatment in childhood epilepsy: age-dependent factors. *No To Hattatsu*. 2000; 32(1): 15-20 (in Japanese with English abstract).
- 3) Senf P, Schmitz B, Holtkamp M, et al. Prognosis of juvenile myoclonic epilepsy 45 years after onset: seizure outcome and predictors. *Neurology*. 2013; 81(24): 2128-2133.

■ Search formula and secondary reference sources

PubMed search: December 13, 2015

(((((“epilepsy” [MeSH Terms] OR “epilepsy” [All Fields]) AND (“therapy” [Subheading] OR “therapy” [All Fields] OR “therapeutics” [MeSH Terms] OR “therapeutics” [All Fields])) AND (“recurrence” [MeSH Terms] OR “recurrence” [All Fields])) OR (“recurrence” [MeSH Terms] OR “recurrence” [All Fields] OR “relapse” [All Fields])) AND (“risk factors” [MeSH Terms] OR (“risk” [All Fields] AND “factors” [All Fields]) OR “risk factors” [All Fields] OR (“risk” [All Fields] AND “factor” [All Fields]) OR “risk factor” [All Fields]) AND type [All Fields] AND (“syndrome” [MeSH Terms] OR “syndrome” [All Fields])) = 349. Finally the above references were included.

Is there an optimal dose reduction speed of antiepileptic drugs?

Summary

There is no reliable evidence for recommendation of the optimal speed for dose reduction of antiepileptic drugs for both children and adults.

Comment

According to a Cochrane review¹⁾ that verified the risk of seizure relapse in a rapid withdrawal group that terminated treatment within a tapering period of 3 months and a slow withdrawal group with a longer tapering period, there was no such study in adults. There were several studies in children. However, no conclusion could be derived because of issues such as deficient methodology and insufficient sample size. Even in children, there is no evidence that can be reflected in guideline.

In principle, we should taper the dose gradually. Abrupt cessation of the antiepileptic drugs has the risk of causing unexpected rebound seizure or status epilepticus. Especially, phenobarbital and clonazepam should be tapered carefully.

■ References

- 1) Ranganathan LN, Ramaratnam S. Rapid versus slow withdrawal of antiepileptic drugs. *Cochrane Database Syst Rev.* 2006; (2): CD005003.

■ Search formula and secondary reference sources

PubMed search: December 13, 2015

("epilepsy" [MeSH Terms] OR "epilepsy" [All Fields]) AND ("therapy" [Subheading] OR "therapy" [All Fields] OR "therapeutics" [MeSH Terms] OR "therapeutics" [All Fields]) AND ("anticonvulsants" [Pharmacological Action] OR "anticonvulsants" [MeSH Terms] OR "anticonvulsants" [All Fields] OR "anticonvulsant" [All Fields]) AND ("appointments and schedules" [MeSH Terms] OR "appointments" [All Fields] AND "schedules" [All Fields]) OR "appointments and schedules" [All Fields] OR "schedule" [All Fields]) AND withdrawal [All Fields] AND discontinuation [All Fields] = 27. Finally the above reference was included.

What are the poor prognostic factors in treatment termination?

Summary

The risk of seizure recurrence is high in patients with adolescent-onset epilepsy, symptomatic epilepsy, and EEG abnormalities.

In adult-onset epilepsy, the following factors increase the risk of recurrence: (1) taking two or more drugs at the onset of dose reduction, (2) a history of tonic-clonic seizure, (3) a history of myoclonic seizure, and (4) neurological abnormalities.

Comment

Berg and Shinnar¹⁾ conducted a detailed meta-analysis on the predictors of poor prognosis related to treatment withdrawal in childhood and adult epilepsy. The risk of recurrence in the first year after tapering of antiepileptic drug was 0.25 (0.21–0.30) and the risk of recurrence in the second year was 0.29 (0.24–0.34). The risk factors were as follows. Adolescent onset epilepsy had a higher recurrent risk compared to childhood onset epilepsy [relative risk 1.79 (1.46–1.81)]. Adult onset epilepsies had a higher recurrent risk compared to childhood onset epilepsies [relative risk 1.34 (1.00–1.81)]. Symptomatic epilepsy had a higher recurrent risk compared to idiopathic epilepsy [relative risk 1.55 (1.21–1.98)]. Especially, symptomatic epilepsy with motor symptoms had a higher risk of recurrence compared to idiopathic epilepsy [relative risk 1.79 (1.13–2.83)]. Patients with abnormal EEGs had a relative risk of 1.45 (95% CI, 1.18 to 1.79) compared to those with normal EEGs. There was no adequate evidence regarding the degree of abnormalities in EEG.

In a randomized controlled trial (RCT) of 1,013 adult epilepsy patients who had been seizure-free for more than 2 years, the risk of recurrence was higher in patients who took two or more drugs or those with a history of tonic-clonic seizure²⁾. Based on this study, a prognostic index for recurrence of seizures after remission of epilepsy was developed³⁾. A study on the consequences of treatment termination in adult epilepsy pointed out that recurrence rate was higher in patients with neurological signs⁴⁾.

According to a review on recurrence after treatment termination in adults and children⁵⁾, seizures remitted again in most of the patients by restarting the drugs, but in 19% of the patients (mean of 14 studies, 95% CI: 15–24%), remission was not obtained by resuming the drugs, and 23% of them became refractory. The factors inducing intractable recurrence included symptomatic etiology, partial epilepsy, and cognitive impairment.

■ References

- 1) Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. *Neurology*. 1994; 44(4): 601-608.
- 2) Medical Research Council Antiepileptic Drug Withdrawal Study Group. Randomised study of antiepileptic drug withdrawal in patients in remission. *Lancet*. 1991; 337(8751): 1175-1180.
- 3) Medical Research Council Antiepileptic Drug Withdrawal Study Group. Prognostic index for recurrence of seizures after remission of epilepsy. *BMJ*. 1993; 306(6889): 1374-1378.
- 4) Lossius MI, Hessen E, Mowinckel P, et al. Consequences of antiepileptic drug withdrawal: A randomized, double-blind study (Akershus Study). *Epilepsia*. 2008; 49(3): 455-463.
- 5) Schmidt D, Löscher W. Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. *Acta Neurol Scand*. 2005; 111(5): 291-300.

■ Search formula and secondary reference sources

PubMed search: December 13, 2015

("epilepsy" [MeSH Terms] OR "epilepsy" [All Fields]) AND ("therapy" [Subheading] OR "therapy" [All Fields] OR "therapeutics" [MeSH Terms] OR "therapeutics" [All Fields]) AND ("therapy" [Subheading] OR "therapy" [All Fields] OR "treatment" [All Fields] OR "therapeutics" [MeSH Terms] OR "therapeutics" [All Fields]) AND ("prognosis" [MeSH Terms] OR "prognosis" [All Fields]) AND outcome [All Fields] AND termination [All Fields] = 83. Finally the above references were included.

Should driving be avoided during dose reduction of antiepileptic drugs?

Summary

The Road Traffic Act revised in 2013 and later contains no regulation concerning driving motor vehicles during dose reduction of antiepileptic drugs.

The “Guidelines for assessing fitness of driving for people with epilepsy”¹⁾ produced by the Japan Epilepsy Society Legal Issue Committee in 2001 claimed the following: When antiepileptic drugs are being reduced or stopped following the instructions of a doctor, the patients are prohibited from driving a motor vehicle during the period of dose reduction and for three months after the end of dose reduction. Thereafter, the “Proposal for Epilepsy and Driving”²⁾ also produced by the same Committee proposed no driving and observation for 6 months after the end of dose reduction or termination of treatment, except when there is sufficient evidence that there is no risk of recurrence (long seizure-free period, small total number of attacks, epilepsy syndrome with low risk of recurrence, patients with good prognosis after epilepsy surgery).

■ References

- 1) Japan Epilepsy Society Legal Issue Committee. Guidelines for assessing fitness of driving for people with epilepsy. Tenkan Kenkyu. 2001; 19(2): 140-141 (in Japanese).
- 2) Japan Epilepsy Society Legal Issue Committee. “Proposal for epilepsy and driving” (2014) <http://square.umin.ac.jp/jes/images/jes-image/driveteigen2.pdf> (in Japanese).

■ Search formula and secondary reference sources

PubMed search: December 13, 2015

(“epilepsy” [MeSH Terms] OR “epilepsy” [All Fields]) AND (“therapy” [Subheading] OR “therapy” [All Fields] OR “therapeutics” [MeSH Terms] OR “therapeutics” [All Fields]) AND (“automobile driving” [MeSH Terms] OR (“automobile” [All Fields] AND “driving” [All Fields]) OR “automobile driving” [All Fields]) AND (“jurisprudence” [MeSH Terms] OR “jurisprudence” [All Fields] OR “law” [All Fields]) = 93. Finally the above references were included.