




---

## Honing in on Risk Factors for Prolonged Remission Off Medication by Reducing Heterogeneity

---

### Complete Remission in Nonsyndromic Childhood-Onset Epilepsy.

Anne T. Berg, Francine M. Testa, Susan R. Levy. *Ann Neurol* 2011;70:566–573.

**OBJECTIVE:** Determine the probability of attaining complete remission in children with nonsyndromic epilepsy (NSE) over the course of  $\geq 10$  years from initial diagnosis; identify early predictors of complete remission; and assess the risk of relapse after achieving complete remission. **METHODS:** In a prospective community-based cohort, complete remission was defined as 5 years seizure-free and medication-free. Any subsequent seizure for any reason was a relapse. Univariate and bivariate analyses were conducted with standard methods including the Kaplan-Meier approach. Proportional hazards modeling was used for multivariable analysis. **RESULTS:** Of 613 cohort members, 347 had NSEs, of whom 294 (85%) were followed  $\geq 10$  years (maximum = 17.9). A total of 170 in 294 (58%) achieved complete remission, 10 of whom (6%) relapsed. Seizure outcome at 2 years (remission, pharmacoresistant, unclear;  $p < 0.0001$ ) and underlying cause ( $p < 0.0001$ ) distinguished groups with complete remission ranging from  $\sim 20\%$  to  $\sim 75\%$ . Older age at onset was independently associated with a poorer chance of complete remission. Relapses occurred up to 7.5 years after attaining complete remission and were marginally associated with underlying cause ( $p = 0.06$ ). **INTERPRETATION:** Complete remission occurs in over one-half of young people with NSE and generally persists. Meaningful but imperfect predication is possible based on underlying cause and early seizure control. The finding of age effects may play a role in meaningful identification of phenotypes, which could become fruitful targets for genetic and imaging investigations in these otherwise poorly differentiated epilepsies.

### Commentary

The study by Berg et al. presents the risk and risk factors for complete remission in children without electroclinical syndromes, developmental encephalopathies, and potential electroclinical syndromes that could not be well classified who were observed for at least 10 years. Such nonsyndromic epilepsy represents almost 60% of childhood-onset epilepsy. Taking this interesting approach permits an evaluation of the cumulative risk for remission, risk factors, and risk for relapse absent children with electroclinical syndromes, in which the prognosis is part of the definition. The remaining cohort of nonsyndromic epilepsy is a mixture of epilepsy of unknown cause and epilepsy caused by structural or metabolic factors and more closely mirrors epilepsy in adults, permitting better comparisons of risk factors for remission across the lifespan. Restriction in this manner also hones the risk factors for remission that are identified, providing more valid estimates of the magnitude of risk associated with these factors.

In this study, remission is defined as at least 5 years free of seizures off medication and is called complete remission, not because it is the final endpoint for all children meeting criteria,

but because it is a clinically meaningful endpoint that endures for most until the current time. This definition of remission has been used before by others, although it has not previously been called complete remission (1, 2). The more commonly used definition is 5 years free of seizures with or without medication (1–6), perhaps because, as pointed out in the paper, decisions to stop medication are multifactorial. In contrast, 5 years free of seizures can be observed uniformly across all people with epilepsy.

Another facet that separates this study from others is the availability of MRI exams in almost 90% of all nonsyndromic epilepsy observed for 10 years or more. Among these, 21% had an MRI abnormality. A prior publication of the Connecticut cohort has reported imaging in almost 80% of the full cohort, with abnormal imaging rare but present (3.5%) in children who were clinically normal and with abnormal imaging more common (12.7%) in the full cohort (7). These findings suggest that most, but not all, of the MRI abnormalities examined in the current report represent overlap with underlying brain disorder, abnormal neurologic examination, intellectual disability only, or autism spectrum disorder.

The occurrence of complete remission and risk factors for complete remission are examined in those with nonsyndromic epilepsy who were observed for 10 or more years. Others have also evaluated risk factors for remission in epilepsy cohorts observed for this long, including studies in Finland (5, 8),



the United Kingdom (3), Holland (9), Canada (8), Sweden (4), and the United States (1); however, not all of these studies observed remission without medication or observed 5-year remission. Examining a minimum of 5 years in remission without medication instead of a minimum of 5 years regardless of remission on or off medication decreases the likelihood of relapse and thus improves the identification of risk factors for complete remission. This is true even if there is misclassification of children in 5-year remission on medication who could have achieved complete remission off medication but who were not withdrawn from medication because either they, their parents, or their physician did not support medication withdrawal. As previously reported by Annegers et al. (1), the risk for relapse in the Connecticut cohort was small—approximately 1% per year in those free of seizures for 5 years while off medication.

Early seizure outcome, evidence of underlying brain disorder, age at onset of epilepsy, status epilepticus, convulsive seizures, history of febrile seizures, first-degree family history of epilepsy, and initial seizure frequency were examined as risk factors for complete remission. In the final adjusted model, predictors of complete remission included evidence of underlying brain disorder, age <10 years at onset of epilepsy, and lack of early seizure remission. Not surprisingly, each of these risk factors has been identified in other studies of children (2, 8, 9) studies of children and adults (1, 3, 6). Importantly, other risk factors for 5-year remission on or off medication that were previously identified by others—such as seizure type (1, 3), epileptiform abnormality on EEG (2), lack of neonatal seizures (8)—were not identified in the unadjusted analysis of the current study. Their absence may be due to the longer length of follow-up of the current cohort, the focus on nonsyndromic epilepsy, or other unknown factors. The longer length of follow-up is an unlikely explanation that is supported by the comparisons made between those observed for at least 10 years and those not observed for as long.

The merit of this analysis is that it was designed to decrease the heterogeneity of examinations of remission in childhood-onset epilepsy, but heterogeneity remains because of the known strong associations between evidence of underlying brain disorder (i.e., structural or metabolic etiology) and decreased risk for remission (1, 10). This leads to an important question for future examinations of risk factors for remission. Do risk factors for complete remission (or remission generally) differ according to etiology of nonsyndromic epilepsy? This is explored briefly in the current paper during examination of the association between early seizure outcome and complete remission separately for those with underlying structural or metabolic etiology and those with unknown cause. Early seizure outcome is associated with remission when stratified by etiology, which is the same relationship observed in the combined etiologies. However, this may not be the case for all factors, such as status epilepticus, which was significant in unadjusted analysis but not in adjusted analysis, as well as for

other risk factors examined that were not significant in unadjusted analysis that included all nonsyndromic epilepsy.

In the end, parents and children want to know if seizures will cease for a long enough time to be considered practically cured. The same care that is taken to create as meaningfully homogeneous a cohort as possible for the identification of genetic etiology should be taken for examination of epilepsy outcome. Studying cohorts of epilepsy more homogeneous for their etiology, and perhaps etiology and seizure type, may improve the identification of predictors of complete remission and remission generally. Numbers in any one study may be too small, but there remains potential for combining cohorts and determining seizure type and etiology by consensus to move further in the direction anticipated by this analysis. It is useful for us as researchers and may lead to potential interventions, such as more early surgery. Moreover, it is crucial for people with epilepsy and their families, who deserve to understand the course of the disorder.

by Dale C. Hesdorffer, PhD

#### References

1. Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. *Epilepsia* 1979;20:729–737.
2. Arts WFM, Brouwer OF, Boudewijn Peters AC, Stroink H, Peeters EAJ, Schmitz PIM, van Donselaar CA, Geerts AT. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. *Brain* 2004;127:1774–1784.
3. Cockerell OC, Johnson AL, Sander JWAS, Shorvon SD. Prognosis of epilepsy: A review and further analysis of the first nine years of the British national general practice study of epilepsy, a prospective population-based study. *Epilepsia* 1997;38:31–46.
4. Lindsten H, Stenlund H, Forsgren L. Remission of seizures in a population-based adult cohort with newly diagnosed unprovoked epileptic seizure. *Epilepsia* 2001;42:1025–1030.
5. Sillanpaa M, Schmidt D. Natural history of treated childhood-onset epilepsy: Prospective, long term population-based study. *Brain* 2006;129:617–624.
6. MacDonald BK, Johnson AL, Goodridge DM, Cockerell OC, Sander JWAS, Shorvon SD. Factors predicting prognosis of epilepsy after presentation with seizures. *Ann Neurol* 2000;48:833–841.
7. Berg AT, Testa FM, Levy SR, Shinnar S. Neuroimaging in children with newly diagnosed epilepsy: A community-based study. *Pediatrics* 2000;106:527–532.
8. Sillanpaa M, Camfield PR, Camfield CS. Predicting long-term outcome of childhood epilepsy in Nova Scotia, Canada and Turkey, Finland: Validation of a simple scoring system. *Arch Neurol* 1995;52:589–592.
9. Geerts AT, Arts WFM, Stroink H, Peeters E, Brouwer O, Peters B, Laan L, van Donselaar C. Course and outcome of childhood epilepsy: A 15-year follow-up of the Dutch study of epilepsy in childhood. *Epilepsia* 2010;51:1189–1197.
10. Cockerell OC, Johnson AL, Sander JWAS, Hart YM, Shorvon SD. Remission of epilepsy: Results from the National General Practice Study of epilepsy. *Lancet* 1995;346:140–144.



# American Epilepsy Society

## *Epilepsy Currents Journal*

### Disclosure of Potential Conflicts of Interest

#### **Instructions**

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

#### **1. Identifying information.**

Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

#### **2. The work under consideration for publication.**

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

#### **3. Relevant financial activities outside the submitted work.**

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### **4. Other relationships**

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



# American Epilepsy Society

## Epilepsy Currents Journal

### Disclosure of Potential Conflicts of Interest

#### Section #1 Identifying Information

1. Today's Date: March 7, 2012
2. First Name Dale Last Name Hesdorffer Degree PhD
3. Are you the Main Assigned Author?  Yes  No

If no, enter your name as co-author:

4. Manuscript/Article Title: Honing in on Risk Factors for Prolonged Remission Off Medication by Reducing Heterogeneity
5. Journal Issue you are submitting for: 12.3

#### Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship just add rows to this table.

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Grant	<input type="checkbox"/>		\$35,880.00	NINDS	I work on other aspect of Dr. Berg's grant
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>				
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>				
4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input type="checkbox"/>				
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>				
6. Provision of writing assistance, medicines, equipment, or administrative support.	<input checked="" type="checkbox"/>				
7. Other	<input checked="" type="checkbox"/>				

\* This means money that your institution received for your efforts on this study.

\*\* Use this section to provide any needed explanation.

**Section #3 Relevant financial activities outside the submitted work.**

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

Type of relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Board membership	<input checked="" type="checkbox"/>				
2. Consultancy	<input type="checkbox"/>	12,000.00		Mount Sinai Medical Center	Consultant on grant (not epilepsy related)
3. Employment	<input checked="" type="checkbox"/>				
4. Expert testimony	<input checked="" type="checkbox"/>				
5. Grants/grants pending	<input type="checkbox"/>			NINDS, NICHD, CDC, AUCD	There are many grants.
6. Payment for lectures including service on speakers bureaus	<input checked="" type="checkbox"/>				
7. Payment for manuscript preparation.	<input checked="" type="checkbox"/>				
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>				
9. Royalties	<input checked="" type="checkbox"/>				
10. Payment for development of educational presentations	<input type="checkbox"/>				
11. Stock/stock options	<input checked="" type="checkbox"/>				
12. Travel/accommodations/meeting expenses unrelated to activities listed.**	<input type="checkbox"/>	4,000.00		GSK	Travel to present a paper on unpaid work I do with them
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>				

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

**Section #4 Other relationships**

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest.  
 Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.

