



## Two Populations Are Better Than One

### Distribution of Febrile Seizure Duration and Associations with Development.

Hesdorffer DC, Benn EKT, Bagiella E, Nordli D, Pellock J, Hinton V, Shinnar S; for the FEBSTAT Study Team. *Ann Neurol* 2011;70:93–100.

**OBJECTIVE:** In prior studies of febrile seizures (FSs), prolonged FSs were defined, absent empirical evidence, as lasting 10 or 15 minutes or more. We assessed the distribution of FS duration in a cohort with first FSs, and the association between FS duration and baseline characteristics of the children. **METHODS:** We calculated the observed cumulative probability,  $S(t)$ , that a FS would last at least  $t$  minutes,  $S(t) = \exp(-t/\tau)$ . Data were also fit using a model obtained as the sum of 2 exponential distributions ( $S[t] = \alpha \exp[-t/\tau_1] + [1 - \alpha] \exp[-t/\tau_2]$ ). After assessing the best fit, the cutoff defining long FS was determined. Logistic regression was used to examine associations between long FSs and baseline characteristics, behavior, and development. **RESULTS:** In 158 children with a first FS, median duration was 4.0 minutes. Duration of FS was best fit by a 2-component mixture exponential model. Using this model, we identified 1 population that accounts for 82.3% of FSs and has a mean duration of 3.8 minutes (short FS) and a second population that accounts for 17.7% of FSs and has a mean duration of 39.8 minutes (long FS). Long FSs were significantly associated with developmental delay ( $p = 0.010$ ) and delays and younger age at first FS ( $p = 0.048$ ). **INTERPRETATION:** Like the distribution of afebrile seizure duration in children, the distribution of first FS duration is best modeled by assuming 2 populations. Developmental delay and younger age are associated with prolonged FSs. Our data lend further support to defining 10 minutes as the upper limit for a simple FS.

### Commentary

Given that febrile seizures (FSs) are the most common seizure “syndrome” of childhood occurring in 2 to 4 percent of individuals, one would think that clear definitions and descriptors based upon data are available. However, when one digs not very far below the surface, one finds some fundamental gaps. In 1980, the National Institutes of Health (1) convened a consensus conference to approach a number of critical questions such as, “What is a febrile seizure?” as well as attendant risks (injury, repeat febrile and afebrile seizures, benefits and risks of prophylaxis and management). The consensus suggested that these seizures usually occurred between 3 months and 5 years, but otherwise did not provide guidance as to how long the seizures last or any basis for distinguishing those that were prolonged from those that were not. However, a prolonged seizure was identified as one of the important risk factors predisposing the child to afebrile seizures. One of the seminal studies upon which this recommendation was based (and which we have used to counsel our families) defined prolonged as greater than 15 minutes and reported that this will occur in almost 8 percent of children with FS (2). The use of 10 to 15 minutes as the cut-point to identify seizures as prolonged has been adopted by subsequent reports (3–6).

What are the implications embedded in the concept of a cut-point? A meaningful risk factor for afebrile seizures? A marker for current and/or future developmental delay? Does it reveal something about the neurobiology of seizure pathophysiology, and, specifically, termination? The answers to these questions can play a role in how we evaluate children with FS, considerations for acute and prophylactic therapies (especially if anti-epileptogenesis agents become available), referral for developmental services, and creation of novel treatments based on known (and perhaps common) pathophysiology. So determining seizure duration is not a trivial matter, and the accuracy of 10 to 15 minutes becomes crucial. So how long do FSs really last? If you ask family members who witnessed the event, “It seemed like forever” may be the most common response. Is there any real data? The answer is “Yes,” but only very recently.

Hesdorffer et al. (4) prospectively ascertained children with a first FS from the emergency department logs and hospital discharges in a metropolitan medical center spanning the years 1999 to 2004 (4). Information regarding seizure duration and developmental status was obtained from the medical record and parent interviews, in addition to patient demographics and family history. Subsequently, an MRI and formal developmental testing were performed on each child. A total of 158 patients with “complete data on exact seizure duration” were studied. Visual analysis of the plotted seizure durations suggested at least two populations of durations, with the transition point occurring at approximately 10 minutes. In fact,



the data were best fit by a two-exponential model, with mean seizure durations of 3.8 minutes and 39.8 minutes accounting for 82 percent and 18 percent of the seizures, respectively. Although there is significant overlap in the populations (as the authors point out), the clear separation provides evidence-based confirmation of the clinical observation that seizures greater than 10 to 15 minutes may represent a biologically different population of children. Furthermore, these population means are remarkably similar to those estimated for children with first unprovoked seizures of 3.6 and 31 minutes accounting for 76 percent and 24 percent of the studied cohort, respectively (7). Although the patients were of different age ranges and from very different populations, one cannot help but wonder if very important information regarding seizure termination “kinetics” has been revealed. This could provide a framework for studying biologically plausible mechanisms of seizure termination in animal models.

The study also provided predictive information as to which child is likely to have a prolonged FS. Children with younger age and delayed motor milestones were significantly more likely to have longer seizures, a finding confirmed by formal developmental testing after the seizure. The latter finding is consistent with previous studies indicating developmental delay as a risk factor for FSs, febrile status epilepticus, and afebrile seizures. It will be of interest to learn the long-term cognitive outcome of these different populations of children.

The study by Hesdorffer et al. (4) highlights the important insights that can be gained by the collection and careful analysis of the individual phenotypic features of seizures. This need is reflected in the formation by the National Institutes of Health Common Data Elements (CDEs) Epilepsy Workgroup. This group was convened for the purpose of creating CDEs to be used in case report forms (CRFs) for epilepsy-related studies (8). The work product can be viewed on the NIH website (<http://www.commondataelements.ninds.nih.gov/Epilepsy.aspx>) and is organized into a series of Epilepsy CDE Standards, one of which describes the CDEs for the Classification of Seizures, Etiologies, and Syndromes. However, there is no mention of the precise data elements that go into the diagnoses (i.e., semiology, duration, frequency). Rather, the assumption is made that a seizure of defined type has occurred and that the specific features are embedded in seizure or syndrome classification.

It could be argued that if this is to be the place where data standards are recommended, the fundamental semiologic descriptors must be specified if a true data dictionary is to be created. What would this look like for the data element duration? First, the *units* would need to be specified; fortunately, seconds and minutes are universal. The next issue would be the *method* by which the measurement was made—the report

that a time-keeping device (watch, clock) was used to document onset and termination of the seizure would be optimal. If estimation is all that is available, then the reliability of the observer—that is, medical health provider (physician, nurse, paramedic, family member)—would need to be assessed. This estimation of time is derived from memory, which is recognized to be a complex process (9) and has only recently been tractable to direct measurement (10). Finally, it must be recognized that the observed duration is only an approximation without EEG confirmation. It is recognized that the seizure may be measured differently in the epilepsy monitoring unit (EMU) as onset and termination may be different electrically than clinically. The latter standard could certainly be applied to EMU-based studies. The current study illustrates the importance of collecting phenotypic data in a prospective, standardized manner in defining evidence-based features that are useful as risk factors and potentially giving insight into our thinking about common pathophysiologic mechanisms.

by Jeffrey Buchhalter, MD, PhD

#### References

1. Freeman JM. Febrile seizures: A consensus of their significance, evaluation, and treatment. *Pediatrics* 1980;66:1009–1012.
2. Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. *N Engl J Med* 1976;295:1029–1033.
3. Annegers JF, Hauser WA, Elveback LR, Kurland LT. The risk of epilepsy following febrile convulsions. *Neurology* 1979;29:297–303.
4. Hesdorffer DC, Benn EK, Bagiella E, Nordli D, Pellock J, Hinton V, Shinnar S. Distribution of febrile seizure duration and associations with development. *Ann Neurol* 2011;70:93–100.
5. Shinnar S, Pellock JM, Berg AT, O'Dell C, Driscoll SM, Maytal J, Moshe SL, DeLorenzo RJ. Short-term outcomes of children with febrile status epilepticus. *Epilepsia* 2001;42:47–53.
6. Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. *N Engl J Med* 1998;338:1723–1728.
7. Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? *Ann Neurol* 2001;46:659–664.
8. Loring DW, Lowenstein DH, Barbaro NM, Fureman BE, Odenkirchen J, Jacobs MP, Austin JK, Dlugos DJ, French JA, Gaillard WD, Hermann BP, Hesdorffer DC, Roper SN, Van Cott AC, Grinnon S, Stout A. Common data elements in epilepsy research: Development and implementation of the NINDS epilepsy CDE project. *Epilepsia* 2011;52:1186–1191e-pub.
9. Friedman WJ. *About Time: Inventing the Fourth Dimension*. Cambridge, MA: MIT Press, 1990.
10. Smith AB, Giampietro V, Brammer M, Halari R, Simmons A, Rubia K. Functional development of fronto-striato-parietal networks associated with time perception. *Front Hum Neurosci* 2011;5:136.



# 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: 4/13/2012
2. First Name Jeffrey Last Name Buchhalter Degree MD, PHD
3. Are you the Main Assigned Author?  Yes  No

If no, enter your name as co-author:

4. Manuscript/Article Title: Distribution of Febrile Seizure Duration and Associations with Development
5. Journal Issue you are submitting for: Epilepsy Currents

#### 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 checked="" type="checkbox"/>				
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 checked="" 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 checked="" type="checkbox"/>				
3. Employment	<input checked="" type="checkbox"/>				
4. Expert testimony	<input checked="" type="checkbox"/>				
5. Grants/grants pending	<input checked="" type="checkbox"/>				
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 checked="" type="checkbox"/>				
11. Stock/stock options	<input checked="" type="checkbox"/>				
12. Travel/accommodations/meeting expenses unrelated to activities listed.**	<input checked="" type="checkbox"/>				
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.  
Epilepsy Currents Editorial Board