ARTICLE

Temperature, Age, and Recurrence of Febrile Seizure

Margriet van Stuijvenberg, MD; Ewout W. Steyerberg, PhD; Gerarda Derksen-Lubsen, MD, PhD; Henriëtte A. Moll, MD, PhD

Objective: Prediction of a recurrent febrile seizure during subsequent episodes of fever.

Design: Study of the data of the temperatures, seizure recurrences, and baseline patient characteristics that were collected at a randomized placebo controlled trial of ibuprofen syrup to prevent febrile seizure recurrences.

Setting: Two pediatric hospitals in the Netherlands.

Patients: A total of 230 children with an increased risk of febrile seizure recurrence.

Main Outcome Measure: Seizure recurrence during a subsequent fever episode.

Results: A total of 509 episodes of fever were registered with 67 recurrences; 35 (52%) recurrences within the first 2 hours after fever of onset had a lower median temperature (39.3°C) than 32 (48%) after more than 2 hours of fever (40.0°C, $P<.001$). Poisson regression analysis resulted in 3 univariably significant ($P<.05$) predictors of a recurrence of seizure during a subsequent episode of fever. In a multivariable model, they were corrected for their correlation: interval between the last previous seizure and fever of onset less than 6 months (relative risk = 1.3 [95% confidence interval: 0.8-2.4]), age at fever of onset (relative risk = 0.7 [95% confidence interval: 0.5-1.0] per year increase) and temperature at fever of onset (relative risk = 1.7 [95% confidence interval: 1.1-2.8] per degree Celsius increase).

Conclusions: Half of the recurrent seizures occur in the first 2 hours after fever of onset of a subsequent fever episode. If seizure recurs at a later time, the temperature at seizure is higher compared with recurrences occurring in the first 2 hours of fever. Young age at fever of onset, high temperature at fever of onset, and high temperature during the episode of fever are associated with an increased risk of a recurrent febrile seizure at the moment that a child with a history of febrile seizures has fever again.

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Editor's Note: This study adds considerable data to the current relative paucity of data on what predicts multiple febrile seizures within a given febrile illness. Get that temperature down immediately after the first seizure, especially in younger children.

Catherine D. DeAngelis, MD

From the Departments of Pediatrics, Sophia Children's Hospital (Drs van Stuijvenberg and Moll), Rotterdam, and Juliana Children's Hospital (Dr Derksen-Lubsen), Den Haag; and the Department of Public Health, Erasmus University (Dr Steyerberg), Rotterdam, the Netherlands.

DURING THE last decade, several risk factors for recurrence of seizure in children affected by febrile seizures have been defined. These include young age at onset, family history of febrile seizures, previous recurrent febrile seizures, a less than 6-month time lapse since previous seizure, a low temperature (<40.0°C) at the initial febrile seizure, and a multiple-type initial febrile seizure.[1-6] Furthermore, frequent episodes of fever have shown to be associated with an increased risk of recurrent febrile seizures.[7,8] However, it is also of practical interest to predict recurrence of a febrile seizure during subsequent episodes of fever. To our knowledge, this has never been investigated. An episode of fever is, in fact, the only time that the child is at risk to suffer from a recurrent febrile seizure.[9] The body temperature during an episode of fever has been reported to play a role in the development of a febrile seizure.[10,11] Further, the risk of recurrence of seizure decreases with age.[4,6] In this study, we aim to clarify the effects of these and other previously reported risk factors for recurrence of seizure. Therefore, we have examined the temperatures during fever and the baseline patient characteristics of 230 children with febrile seizures who participated in a randomized double blind placebo controlled trial of ibuprofen syrup to prevent recurrences of febrile seizure.[12] We report the analysis of factors that predict recurrence of a seizure during subsequent episodes of fever.

PATIENTS AND METHODS

PATIENTS

We used the prospectively collected data of 230 patients who participated in a randomized controlled trial of ibuprofen syrup to prevent recurrent febrile seizures. To be eligible for the study, children had to be between 1 and 4 years of age and had to have an increased risk of recurrence of febrile seizure as defined by the presence of one or more of the following characteristics: first-degree family history of febrile seizures, temperature below 40.0°C at the initial seizure, multiple-type initial febrile seizure, and previous recurrent febrile seizures.[1,2,5,6] Children currently using antiepileptic drugs, including intermittent diazepam, were excluded. Children were assigned to either ibuprofen 20 mg/mL, 0.25 mL per kilogram of body weight per dose to be administered every 6 hours at the time of fever (n = 111), or placebo (n = 119).[12] A febrile seizure was defined according to the National Institutes of Health consensus statement.[9] The study protocol was approved by the relevant institutional review boards, and the parents of all participants had given written informed consent.

We used the data of all patients who experienced one or more episodes of fever during follow-up, as reported by the parents. Data of children who had not yet reached the temperature of fever according to our definition (>38.4°C) but who were recognized by the parents as feverish and had a temperature of 38.1°C or higher were included in the analysis. Furthermore, although treatment with ibuprofen influences the course of the temperature, we included the patients who either had been allocated to the placebo group or to the ibuprofen group, since the trial showed that ibuprofen syrup in this dose was not effective in the prevention of recurrent febrile seizures.[12]

PROCEDURES

According to the protocol, the parents were instructed to take the rectal temperature immediately when their child seemed ill or feverish and to start administering the study medication if the temperature exceeded 38.4°C. In the present study this moment has been defined as fever of onset. All temperatures were rectally measured (Philips HP5316 thermometer, Philips Eindhoven, the Netherlands). They were instructed not to administer any other antipyretic drug, to continue with administering the study medication, to measure the temperature every 6 hours until the child was afebrile for 24 hours, and to measure the temperature at the recurrence of seizure. If a child had a first recurrence of febrile seizure after study enrollment, the study was stopped for that child and any subsequent episodes of fever were not taken into account. At the first day of fever of onset and after a recurrent febrile seizure, the child was physically examined. Laboratory tests were not performed and no antibiotic treatment started unless indicated by the clinical condition of the child.

STATISTICAL ANALYSIS

The outcome was a recurrence of febrile seizure during a subsequent fever episode.The analysis only included data from patients having at least 1 episode of fever. Therefore, with logistic regression, we ascertained first if there was any difference in the distribution of baseline patient characteristics between the group of children with and those without at least 1 episode of fever during follow-up.[7,8]

Temperatures are given in median values, with their 25th and 75th percentiles in parentheses. We used unpaired and paired nonparametric tests to analyze differences in temperature at fever of onset and at recurrence of seizure.

For the analysis of recurrence of seizure during subsequent episodes of fever, we used 3 types of data. First, we analyzed the baseline characteristics known at study enrollment, including sex, age, and the presence of the known risk factors for recurrence of seizure as demonstrated by previous studies.[1,2,5,6] Second, we considered patient characteristics that were unique for each episode of fever such as age at fever of onset, the interval between the last previous seizure fever of onset, and the temperature at fever of onset.Third, the data of the temperatures that were measured every 6 hours during the febrile condition were used. This analysis considered seizure recurrence in each 6-hour period of fever, using the most up-to-date temperature data available.

We used Poisson regression analysis to assess the risk of recurrence of seizure.[13] For the first and second type of data, the unit of analysis was a febrile episode. For the third type of data, the unit of analysis was a 6-hour period of fever (a stratum). Follow-up time from fever of onset through 24 hours was divided into 4 strata of 6 hours of fever each. The strata included the patient characteristics (such as age, sex, and temperature), the outcome (ie, the first recurrence of febrile seizure for each child after enrollment into the study), and the number of patients at risk (ie, the number of patients still febrile). If patients had a duration of fever of more than 24 hours, we constructed a fifth period that included the remaining hours of fever. We also analyzed recurrence of seizure in a 6-hour period of fever.

We consider the Poisson model suitable because we are studying a relatively rare event (ie, first recurrence of febrile seizure) in an interval that has a different duration for each individual and that consists of one or more separate periods (ie, subsequent episodes of fever). Univariable and multivariable Poisson regression analysis related patient characteristics to recurrence of seizure. Associations were expressed as rate ratios, which we interpreted as relative risks.[13] The level of statistical significance was set at .05. Calculations were performed with SPSS and EGRET software programs.[14,15]

We report the results of the analyses using data of all randomized patients. However, we repeated the analyses using only the data of the patients randomized to placebo to assess whether the patients randomized to ibuprofen biased the results in any way.

RESULTS

Table 1 gives the patient characteristics at study enrollment of all 230 children. There were no clear differences in patient characteristics in the 182 (79%) children with at least 1 episode of fever compared with the 48 (21%) children without a an episode of fever during follow-up.

The parents reported 555 episodes of fever. Forty-six (8%) of the episodes of fever were excluded from the analysis because the parents had not registered any of the

Table 1. Baseline Patient Characteristics of the Study Population at Study Enrollment (n = 230)*

Characteristics	≥1 Episode of Fever During Follow-up (n = 182 [79%])	No Episodes of Fever During Follow-up (n = 48 [21%])	Odds Ratio (95% Confidence Interval)	*P*
Female sex (n = 90 [39%])	71 (39)	19 (40)	1.0 (0.5-1.9)	.94
Age at initial seizure in years, 1.4 (1.1-1.9)†	1.4 (1.0-1.9)	1.6 (1.2-2.2)	0.7 (0.5-1.1)	.17
First-degree family history of febrile seizures (n = 59 [26%])	44 (24)	16 (33)	0.6 (0.3-1.2)	.17
Initial seizure characteristics				
Temperature, <40.0°C (n = 121 [53%])‡	93 (51)	28 (58)	0.7 (0.4-1.4)	.37
Multiple type (n = 87 [38%])	74 (41)	13 (27)	1.8 (0.9-3.7)	.09
Recurrences before study enrollment§				
0 (n = 146 [64%])	111 (61)	35 (73)	Reference category	. . .
1 (n = 61 [27%])	53 (29)	8 (17)	0.8 (0.5-1.2)	.24
≥2 (n = 23 [10%])	18 (10)	5 (10)	1.6 (0.9-2.9)	.15
Risk factors for recurrence of seizure‖				
1 or 2 risk factors (n = 209 [91%])	163 (90)	46 (96)	Reference category	. . .
3 or 4 risk factors (n = 21 [9%])	19 (10)	2 (4)	2.7 (0.6-11.9)	.20
Age, in years, at study enrollment, 1.9 (1.4-2.5)†	1.9 (1.4-2.4)	1.9 (1.4-2.8)	0.8 (0.5-1.2)	.31
Follow-up, in years, 0.8 (0.4-1.4)†	0.8 (0.3-1.5)	0.7 (0.5-1.3)	1.1 (0.7-1.8)	.76

**Unless otherwise indicated, values are given as number (percentage). Ellipses indicate that there is no* P *for a reference category.*
†Values given as median (25th-75th percentiles).
‡Temperature measured at time closest to the time of seizure (documented in the emergency department or in the patient history).
§Initial seizure not counted as recurrence.
‖As described in the "Patients" subsection of the "Patients and Methods" section.

temperature data during follow-up. No recurrences occurred in these excluded episodes of fever. We further analyzed the 509 episodes of fever, in which 67 (13%) recurrences occurred. Thirty-five (52%) recurrences occurred within the first 2 hours after fever of onset compared with 32 (48%) occurring after more than 2 hours of fever. The risk of a recurrence was 7% (35/509) in the first 2 hours after fever of onset and 7% (32/474) after more than 2 hours of fever.

We analyzed the relationship between the temperature and the first recurrence of febrile seizure using all temperature measurements in the 509 episodes of fever. The temperature at recurrence of seizure was variably and relatively low (39.3°C [25th-75th percentiles, 39.0°C-39.8°C]) in recurrences occurring in the first 2 hours compared with recurrences occurring after more than 2 hours of fever (40.0°C [25th-75th percentiles, 39.6°C-40.4°C]), $P<.001$, Mann-Whitney U test).

In addition, we analyzed all temperatures measured in the episodes of fever in which a recurrence of seizure occurred at 2 hours or more after fever of onset (n = 23 with complete temperature data). In those episodes of fever, the temperature at recurrence of seizure (39.6°C [25th-75th percentiles, 39.1°C-40.1°C]) was higher compared with the temperature at fever of onset (39.3°C [25th-75th percentiles, 38.8°C-39.7°C], $P<.01$, paired Wilcoxon test).

Table 2 gives the results of the Poisson regression analysis of recurrence of seizure per episode of fever. Three univariably significant predictors were interval between the last previous seizure and fever of onset, age at fever of onset, and temperature at fever of onset. Age and temperature at fever of onset had similar effects (relative risk = 0.7) after adjustment for the correlation between these 3 characteristics; age at fever of onset lost its statistical significance ($P = .06$). The analysis was repeated using only the data of the episode of fever of the children randomized to placebo and showed similar results.

The **Figure** shows the relationship between age and temperature at fever of onset vs the risk of recurrence of a febrile seizure in the corresponding episode of fever. The figure illustrates that the risk of a recurrence increases with temperature at fever of onset and decreases with age. The lines indicate 4 arbitrarily chosen recurrence risks: 5%, 10%, 20%, and 30%. For example, if the temperature at fever of onset is 40.0°C, a child aged 1 year has a 30% recurrence risk in the corresponding episode of fever. This risk is between 5% and 10% for a 4-year-old child.

Table 3 gives the results of the Poisson regression of recurrence of seizure per 6-hour period of fever. The associations were similar to the associations in the model predicting recurrence of seizure per episode of fever (Table 2). In a multivariable analysis, we included the 3 characteristics that were univariably significant in all analyses. If we included the temperature at onset of each 6-hour period of fever, instead of the temperature at fever of onset, the multivariable relative risk was higher (2.9 vs 2.0) and the P value smaller ($P<.001$ vs $P = .01$). The analysis using only the data of the children randomized to placebo gave similar results (relative risk = 2.5 [95% confidence interval: 1.7-3.9], $P<.0001$, for the temperature at onset of each 6-hour period of fever).

COMMENT

The present study shows that half of the recurrences of febrile seizure during a subsequent episode of fever occur within the first 2 hours of fever. Accordingly, other studies on febrile seizure show that a substantial part of the seizure recurrences occurs early in the episode of fever and that recurrences of febrile seizure are often the presenting symptom of a feverish illness.[16-,18] However,

Table 2. Patient Characteristics and Febrile Seizure Recurrence per Fever Episode (n = 509)*

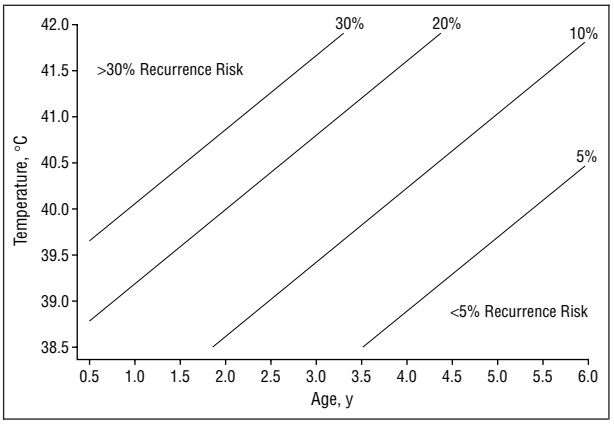
Characteristics	Univariable Analysis		Multivariable Analysis	
	Relative Risk (95% Confidence Interval)	*P*	Relative Risk (95% Confidence Interval)	*P*
Patient characteristics known at study enrollment				
Female sex	1.5 (0.9-2.5)	.09	. . .	. . .
First-degree family history of febrile seizures	0.8 (0.4-1.4)	.42	. . .	. . .
Initial seizure characteristics				
Temperature <40.0°C	1.1 (0.7-1.8)	.65	. . .	. . .
Multiple type	1.6 (1.0-2.5)	.06	. . .	. . .
≥1 Recurrences before study enrollment	0.9 (0.6-1.5)	.76	. . .	. . .
No. of risk factors for recurrence of seizure	1.2 (0.9-1.7)	.28	. . .	. . .
Characteristics unique for each episode of fever				
Interval, y†				
>0.5	Reference category	. . .	Reference category	. . .
≤0.5	1.8 (1.1-2.9)	.02	1.3 (0.8-2.4)	.32
Age, in years, at fever of onset	0.7 (0.5-0.9)	.01	0.7 (0.5-1.0)	.06
Temperature at fever of onset, °C	1.7 (1.1-2.8)	.02	1.7 (1.1-2.8)	.02

*Ellipses indicate variables were not included in the multivariable model.
†Time between last previous seizure and fever of onset in years.

previous studies have not demonstrated that the temperature at recurrence of seizure in the first 2 hours after fever of onset is clearly lower compared with the temperature at recurrences of more than 2 hours after fever of onset. These findings suggest a seizure-provoking effect of either the temperature increase, or the high temperature level that has been reached. Furthermore, it might be that febrile seizures occurring after a short duration of fever are occurring in a different (more vulnerable) type of patient than seizures occurring later on. Follow-up studies may give insight into the consistency of this pattern in the individual patient. At least initial febrile seizures occurring after a short duration of fever are associated with an increased risk of recurrence.[4]

Age plays an important role in the susceptibility of febrile seizures; the risk of recurrence of seizure declines with growing older.[1,2,6,19,20] If there is an individual temperature threshold level above which a febrile seizure will develop, this threshold is influenced by age: as the child grows older, the higher the threshold, the lower the risk. The results of our study are in accordance with these hypotheses and findings: age showed to be associated with a recurrence of seizure, although in the multivariable model the level of statistical significance was not reached ($P = .06$); independent of either being longer at risk, or getting higher temperatures during fever, young age is associated with an increased risk of recurrence.

The other predictor of recurrent febrile seizures is the temperature: per degree Celsius increase in temperature at fever of onset, the risk of a febrile seizure increases with a factor of 1.7 and per degree Celsius increase in temperature measured every 6 hours, the risk is increased 2.9 times. To address any difficulty regarding the interpretation of these findings with respect to the inclusion of children who had been using antipyretic treatment during their episodes of fever, we repeated the Poisson analyses using only the data of children randomized to placebo. No differences were found. Clinical studies in children with febrile seizures have shown that a relatively low temperature (<40.0°C) at the initial seizure is associated with an increased risk of recurrent febrile seizures.[6,10] Accordingly, in a matched case-control study, risk factors for developing an initial febrile seizure have been investigated; the height of the temperature as a characteristic of the acute illness was noted to be an independent risk factor.[21] These studies suggest that a febrile seizure temperature threshold exists and that a higher risk of febrile seizures is related to a lower threshold level. The results of our study support this hypothesis.



Relationship between temperature at fever of onset, age at fever of onset, and the risk of recurrence of a febrile seizure per episode of fever.

In our data set, multiple-type initial febrile seizures was the only baseline characteristic and known risk factor that predicted a recurrence of febrile seizure at the time the child has fever (Table 3). In contrast with this finding, other studies concerning risk factors for recurrence show that multiple-type initial febrile seizures is a relatively weak factor compared with a positive first-degree family history of febrile seizures, a low (<40.0°C) temperature at the initial seizure, one or more previous recurrences, and time lapse since previous seizure not exceeding 6 months.[3,4,6,8] The absence of association between the known risk factors and recurrence of seizure

Table 3. Patient Characteristics and Febrile Seizure Recurrence per 6-Hour Time Interval of Fever (n = 1931)*

Characteristics	Univariable Analysis Relative Risk (95% Confidence Interval)	*P*	Multivariable Analysis† Relative Risk (95% Confidence Interval)	*P*	Multivariable Analysis‡ Relative Risk (95% Confidence Interval)	*P*
Patient characteristics known at study enrollment						
Female sex	1.5 (0.1-1.5)	.10	. . .	. . .	. . .	. . .
First-degree family history of febrile seizures	0.8 (0.5-1.5)	.54	. . .	. . .	. . .	. . .
Initial seizure characteristics						
Temperature, <40.0°C	1.1 (0.7-1.8)	.69	. . .	. . .	. . .	. . .
Multiple type	1.7 (1.1-2.8)	.02	. . .	. . .	. . .	. . .
≥1 Recurrences before study entrollment	0.9 (0.5-1.5)	.64	. . .	. . .	. . .	. . .
No. of risk factors for recurrence of seizure	1.3 (0.9-1.7)	.17	. . .	. . .	. . .	. . .
Characteristics unique for each episode of fever						
Interval, y§						
>0.5	Reference category		Reference category		Reference category	
≤0.5	1.9 (1.1-3.1)	.01	1.4 (0.8-2.5)	.28	1.9 (1.0-3.5)	.04
Age, in years, at fever of onset	0.7 (0.5-0.9)	.01	0.7 (0.5-1.0)	.05	0.8 (0.5-1.1)	.19
Temperature, in °C, at fever of onset	2.0 (1.2-3.2)	.01	2.0 (1.2-3.2)	.01	. . .	. . .
Characteristics unique for each 6-h time interval of fever						
Temperature, in °C, at onset of each 6 h	2.8 (2.0-3.9)	<.001	. . .	. . .	2.9 (2.1-4.0)	<.001

**Ellipses indicate variables were not included in the multivariable model.*
†*Variables included in the multivariable model: time interval, age, and temperature at fever of onset.*
‡*Variables included in the multivariable model: time interval, age at fever of onset and temperature at onset of each 6-h interval of fever.*
§*Time between last previous seizure and fever of onset in years.*

in the present study should not be interpreted as lack of importance of these risk factors. Only children with an increased risk of recurrences of febrile seizure have been included. Selection based on high-risk criteria reduces the power of the study to identify these criteria as high-risk factors. Also, if children with a lower risk of recurrence had been included, the relative risks might have been different and the known risk factors might have been found associated with recurrence of seizure. Further, we have studied recurrent seizures in a different way, ie, the prediction of recurrences specifically at the time the child has fever, which might explain the different results.

One might argue that we found the temperature the most important predictor of recurrence of febrile seizure because some temperature data were missing; high temperatures might have been measured more frequently than low ones. However, it is not likely that this mechanism has caused a bias in our analysis because it is unlikely that measuring the temperature is related to the occurrence of a recurrence of seizure. However, the main limitation of our study is that the data cannot be used to analyze the influence of the rapidity of temperature increase on the risk of recurrence of seizure. For the convenience of the participants in the study, the temperature measurements during fever were scheduled every 6 hours, which was simultaneous with the administration of the study medication, without measurements in between. If continuous data had been available, we might have clarified whether the temperature itself, the rapidity of increase, or both, are the main eliciting factors of febrile seizure.

This study was performed mainly to contribute to the scientific insight regarding fever and febrile seizures. The findings may also have practical implications for the information provided to parents of children affected by febrile seizures. It might be reassuring information for parents to hear that half of the recurrences of febrile seizure occur within the first 2 hours of fever. Thus, after 2 hours of fever, the risk of a recurrent seizure is substantially lower. As the child grows older, the recurrence risk is lessened, even when suffering from fever. The high temperature at fever of onset and during the course of the episode of fever is a more difficult thing to discuss. Prevention of fever rising high may only be reached by the undressing and uncovering of the child. The number of episodes of fever might be reduced by eliminating sources of infection. Antipyretic treatment has not been shown to be effective in preventing recurrences of febrile seizure.[12,22-,24] The underlying cause of the fever may play a role in the ineffectiveness of antipyretics to prevent recurrence of seizure. The cause of the fever either may give rise to a resistance to fever-reducing treatment or may have an inherent provoking effect on a recurrence of febrile seizure.

CONCLUSIONS

We conclude that approximately half of the recurrent seizures occur in the first 2 hours after fever of onset. If the recurrent seizure occurs at a later moment, the temperature at seizure will be higher compared with occurrence of the seizure in the first 2 hours of fever. Furthermore, the risk of a recurrence of febrile seizure, at the moment that a child with a history of febrile seizures has fever again, decreases with age and increases with temperature at fever of onset and temperature during fever.

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Corresponding author: Henriëtte A. Moll, MD, PhD, Sophia Children's Hospital, Room Sp 1543, Dr Molewaterplein 60, 3015 GJ Rotterdam, the Netherlands (e-mail: moll@alkg.azr.nl).

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