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*Evidence based paediatrics***Evidence based management of seizures associated with fever**

Martin Offringa, Virginia A Moyer

THE CASE A previously healthy 19 month old boy was rushed to the emergency department after being found unconscious at home by his mother. As she went to wake him from his afternoon nap she heard a short cry. She found him lying on his back, rigid and unresponsive, with blue lips and apparently not breathing. His breathing and circulation were adequate on arrival in the emergency room. His pulse rate was 110 per minute, blood pressure 100/60 mm Hg, and temperature 39.9°C. The boy was lethargic and confused but seemed to recognise his mother. Apart from a slightly red pharynx there was no obvious focus of infection and no rash. Neck rigidity was difficult to evaluate because he actively resisted examination and refused to sit.

Background

A febrile seizure is defined as a seizure occurring in a neurologically healthy child aged 6 months to 5 years. Simple febrile seizures are brief (under 15 minutes' duration), are generalised, and occur in association with fever and only once during any 24 hours.¹ Seizures occurring with fever are the most common neurological disorder in paediatrics, affecting 2-4% of all children in Britain and the United States.² Children whose seizures are attributable to a central nervous system infection and those who have had a previous afebrile seizure or central nervous system abnormality are not considered to have simple febrile seizures.

Finding the evidence

A number of questions arise in this case. You wonder how likely it is that this boy has meningitis and whether lumbar puncture is necessary. If this is a simple febrile seizure, what is the likelihood of future febrile seizures, epilepsy, or brain damage? You also wonder whether you should begin treatment with anticonvulsants. You wish to use an evidence based approach, so you frame your questions to maximise the yield from searching.

Questions and search strategies

Question 1: In young children with a seizure associated with fever (patient/population, event) what is the probability of bacterial meningitis (outcome)? [baseline risk]

Search: Medline (PubMed: www.ncbi.nlm.nih.gov/entrez/static/clinical.html): Clinical queries→aetiology→sensitivity: "fever and seizures and meningitis"

Question 2: In young children with a seizure associated with fever (patient/population, event) can a normal physical examination and history (intervention/test) reliably exclude bacterial meningitis (outcome)? [diagnosis]

Summary points

Seizures occurring in association with fever affect approximately 4% of all children

In children with a seizure associated with fever the probability of bacterial meningitis is low but not zero (ranging between 0-4%)

A normal physical examination and history make bacterial meningitis highly improbable

After a first febrile seizure the probability of seizure recurrence in subsequent fever episodes is related to age, and is highest between 1 and 3 years

After a first febrile seizure prophylactic treatment with antiepileptic drugs does not decrease the likelihood of future febrile seizures

This is the third in a series of five articles

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Search: Medline(PubMed: www.ncbi.nlm.nih.gov/entrez/query.fcgi): "fever and seizures and meningitis and (clinical signs or diagnosis)"

Question 3: In children with a first febrile seizure (patient/population, event), can prophylactic treatment with antiepileptic drugs (intervention) as compared to no therapy (comparison) decrease the likelihood of future febrile seizures (outcome)? [therapy]

Search: PubMed: Clinical queries→therapy→sensitivity "seizures and fever and recurrence"

Question 4: In children with a first febrile seizure (patient/population, event), what is the likelihood of future febrile or afebrile seizures (outcome)? [prognosis]

Search: PubMed: Clinical queries→prognosis→sensitivity "seizures and fever and epilepsy".

Results**Prevalence of meningitis**

In trying to determine the likelihood of meningitis, you are looking for cross sectional studies or follow up studies of children with seizures and fever that identify children who developed meningitis. Your "clinical queries" search nets 30 articles, most of which are informal reviews and letters. One article, a decision analysis, seems relevant.³ You then click on the "related articles"—the hyperlink next to this reference—and find two more articles which seem to be relevant surveys.^{4,5}

Wears et al reviewed seven studies performed in urban hospital emergency rooms in the United States.⁴ All were retrospective surveys of charts documenting the disease outcome after a seizure with fever. Among 2100 such cases of seizures associated with fever the

overall prevalence of meningitis was 1.2%, ranging from 0-4% in the seven studies. It was not stated, however, whether all children underwent lumbar puncture in these emergency rooms, or whether meningitis was excluded on clinical grounds at follow up.

In the second study, 7% of the children who visited the emergency rooms of two Dutch hospitals with a first seizure associated with fever had either bacterial or viral meningitis.⁵ As this study was done in the hospital setting in a country where general practitioners manage up to 50% of all seizures with fever,^{6 7} its results may not apply to the situation where is no family physician or general practitioner to evaluate the child before referral to hospital.

From these two studies it can be concluded that the prevalence of meningitis among children with seizures and fever in North American paediatric emergency wards is between 1% and 2% and, through selective referral, it may be as high as 7% in a European country. These figures indicate that a large number of "unnecessary" lumbar punctures would be done if lumbar puncture were to be carried out in all children with a seizure associated with fever.

Seizures in "well" children

Your next question is whether a seizure can be the sole manifestation of meningitis in a child who seems otherwise well. You are looking for studies that investigate the relations of various signs and symptoms with meningitis in children with seizures and fever, preferably in the form of likelihood ratios. One study provides sensitivity, specificity, and likelihood ratios for the various clinical indicators of meningitis.⁵ This study tried to identify criteria, based on age, specific clinical indicators, or the results of initial blood tests, that could serve as indications for performing lumbar puncture. Meningitis was diagnosed in 23 (7%) of 309 children aged 3 months to 6 years with a first seizure associated with fever who were seen consecutively in the emergency rooms of two major children's hospitals in the western part of the Netherlands. These 23 children were then compared with a reference group of 69 children with seizures associated with fever but without meningitis, selected at random from the remaining 286 children.

Discriminant factors

Several clinical signs and symptoms were examined for their ability to discriminate between children with and without meningitis. The clinical risk factors shown in table 1 were evaluated. The presence of one or more of the major signs—petechiae, nuchal rigidity, coma—

identified 16 out of the 23 children with meningitis (70%). In the absence of meningitis, these major signs of the disease were not found; the likelihood ratio when any of these signs is present (LR +) is therefore infinite (95% confidence interval 6.0 to ∞) and the probability of meningitis approaches 100% (31 to 100%). In the absence of meningeal irritation, petechiae, or complex features of the seizure there were no cases of meningitis in the study. A child's age, sex, degree of fever, and results of routinely performed blood tests did not have any diagnostic value. The likelihood ratios of the negative and positive tests can separate children into two groups, a group in which the risk of meningitis is very high and lumbar puncture should be done regardless of other history or physical findings, and a group in which the risk of meningitis is low and the need for lumbar puncture will depend on other clinical findings.

Generalisability

The Dutch study was a retrospective review of the medical records of children presenting with a first episode of seizure and fever.⁵ The study population was limited to children aged 3 months to 6 years. The pre-test probability of meningitis would be likely to be different in another population of children. In addition, nuchal rigidity may not be as strong a predictor of meningitis in young as in older children; in this patient population the mean age was 18 months. However, these results indicate that it is very unusual for a child with meningitis to present with only a seizure. Also, a fair number of children without meningitis will present with the risk factors mentioned above—that is, the specificity of these "clinical tests" is far from 100%.

Value of prophylactic treatment

To determine whether prophylactic treatment with an antiepileptic drug or an antipyretic as compared with no treatment decreases the likelihood of future febrile seizures, you are looking for studies in which patients with febrile seizures were randomised to different treatment regimens and followed over time to see how many developed subsequent febrile seizures. Of the 55 articles that result from your search, five papers specifically address your question; they are either meta-analyses of randomised controlled trials^{8 9} or are reports of randomised controlled trials.¹⁰⁻¹²

Newton assessed the efficacy of phenobarbitone and valproate for the prophylactic treatment of febrile convulsions by summarising the results from all eight British clinical trials that were done before 1988.⁸ Data

Table 1 Discriminating ability of combinations of clinical indicators of meningitis among children with a seizure associated with fever. Values are numbers (percentages) unless otherwise indicated

Combination of indicators*	Cases (n=23)	Controls (n=69)	Likelihood ratio (95% CI)	
			Absence of combinations	Presence of combinations
At least one complex feature	17 (74)	26 (38)	0.4 (0.2 to 0.8)	1.9 (1.3 to 2.9)
At least one history feature	18 (78)	32 (46)	0.4 (0.2 to 0.9)	1.7 (1.2 to 2.4)
Either a complex or a history feature	23 (100)	45 (65)	0 (0 to 1)	1.5 (1.3 to 1.8)
At least one major sign	16 (70)	0	0.3 (0.2 to 0.6)	∞ (6.0 to ∞)
At least one minor sign, after exclusion of children with any major signs	5/7 (71)	24 (35)	0.4 (0.1 to 1.4)	2.1 (1.2 to 3.6)

*Features of complex seizures: partial, multiple, or prolonged seizure, (longer than 15 minutes). History features: febrile illness for at least three days, vomiting or drowsiness at home, a physician's visit in the previous 48 hours. "Major" signs of meningitis: petechiae, definite nuchal rigidity, coma. "Minor" signs of meningitis: dubious nuchal rigidity, persisting drowsiness, convulsions or paresis or paralysis on examination in the emergency room.

were pooled and analysed on an intention to treat basis. The overall odds ratio of recurrent febrile seizures for treatment with phenobarbitone was 0.8 and for valproate 1.42. Neither of these results was statistically significant. The author therefore concluded that neither treatment is to be recommended.

A second meta-analysis summarised four published non-British, randomised placebo controlled trials that had been carried out using phenobarbitone to prevent febrile seizures.⁹ The risk of recurrences was lower in children receiving continuous phenobarbitone than placebo (odds ratio 0.54, 95% confidence interval 0.33 to 0.90). On average, eight children would have to be given continuous phenobarbitone prophylaxis for two years to prevent one febrile seizure (number needed to treat = 8.5-27).¹³ However, in view of the adverse effects of phenobarbitone, such as irritability, hyperactivity, somnolence, and possibly diminished cognitive development,¹⁰ the authors of this second review also concluded that phenobarbitone prophylaxis of febrile seizures cannot be recommended.

Treatment in febrile periods only

To avoid the adverse effects of giving antiepileptic drugs for prolonged periods, rapidly acting anticonvulsants given only during fever periods have been used in an attempt to reduce the risk of recurrent febrile seizures. Phenobarbitone given at times of fever has been proved ineffective, probably because of the delay in achieving appropriate serum and tissue concentrations. Thus far, only prophylactic diazepam, given orally or rectally, has been studied in placebo controlled trials.

Diazepam—Rosman et al conducted a randomised, double blind, placebo controlled trial among 406 children with a mean age of 24 months who had had at least one febrile seizure, comparing diazepam (0.33 mg per kg body weight), given orally every eight hours during febrile illnesses, with placebo.¹¹ During a mean follow up of two years, the relative risk of subsequent febrile seizures per person year was 0.56 (0.38 to 0.81). Many parents did not give the treatment as directed, and an analysis restricted to children who had seizures while definitely receiving the study drug showed an 82% reduction in the risk of febrile seizures with diazepam. Between 25% and 30% of the children in the study by Rosman were irritable, lethargic, or ataxic after taking diazepam, which might interfere with parents' and clinicians' ability to distinguish benign childhood febrile illness from more serious disease; one in every 3.5-4 children taking diazepam develops these symptoms (number needed to harm = 3.5-4). The decision to recommend this treatment will depend on balancing these potential harms against the potential benefits to each specific child, and on the family's values.

Ibuprofen—To assess whether antipyretic drugs given intermittently prevent recurrence of febrile seizures, a randomised placebo controlled trial was conducted in the Netherlands.¹² Children aged 1 to 4 years who had at least one risk factor for recurrence of a febrile seizure (see below) were randomly assigned to receive either ibuprofen syrup, 5 mg per kg body weight per dose, or placebo every six hours during fever, defined as a temperature >38.4°C. Median follow up time was 12 months. The relative risks for recurrence in the two groups did not differ significantly.



JOHN GREEN/SPL

Prognosis after first seizure

To address the parents' concerns about the prognosis, you are looking for a large cohort of patients with first simple febrile seizures who have been followed over time to see how many develop recurrent febrile or non-febrile seizures. Your search strategy yields 157 articles, only two of which meet your study design criteria.^{14 15}

In a collaborative study, the individual data from five follow up studies that used similar definitions of febrile seizures and risk factors were pooled and reanalysed to estimate the risk of frequent recurrent seizures and occurrence of complex seizures in previously healthy, untreated children.¹⁴ Of a total of 2496 children with 1410 episodes of recurrent seizures, 32% had one, 15% two, and 7% three or more recurrent seizures after a first febrile seizure; 7% had a complex recurrence. The hazard of recurrent seizures was highest between the ages of 12 and 24 months. A history of febrile or unprovoked seizures in a first degree family member, a relatively low temperature at the first seizure, young age at onset (<12 months), a family history of unprovoked seizures, and a partial initial febrile seizure were all associated with an increased risk of subsequent complex seizures. Although complex features of the first seizure—that is, a seizure which is partial, is multiple, or lasts for more than 15 minutes—have long been thought to predict recurrence, the follow up studies included in this review showed that only multiple initial seizures are associated with an increased risk (1.6-fold) for a first recurrence.¹⁴ Prolonged or focal initial seizures were not associated with this increased risk, as long as they had not led to permanent neurological abnormalities.

Risk factors for the occurrence of unprovoked seizures were assessed in a cohort of 428 children followed prospectively for at least two years from their first febrile seizure.¹⁵ Unprovoked seizures occurred in 26 (6%). Neurodevelopmental abnormalities, complex febrile seizures, and a family history of epilepsy were

Table 2 Summary of the evidence

Question	Type of evidence	Result	Comment
What is the probability of bacterial meningitis after a seizure associated with fever?	Summary of surveys of children seen in accident and emergency departments	0.2%-7.0% depending on health care system and setting	English and Dutch GP referral system will select children with a higher risk to present to accident and emergency departments
Can an unremarkable physical examination and history reliably exclude bacterial meningitis?	Case-control study evaluating risk factors	Meningitis could be ruled out in the absence of focal, prolonged, or multiple seizures, suspicious findings on physical examination (petechiae, signs of circulatory failure, etc), and abnormal neurological findings on physical examination (signs of meningeal irritation and various degrees of coma)	It is very unusual for a child with meningitis to present only with a seizure
Can prophylactic treatment with continuous antiepileptic drugs, intermittent oral diazepam, or an antipyretic decrease the likelihood of future febrile seizures?	Two systematic reviews of randomised trials, two randomised trials	Continuous antiepileptic drugs, intermittent diazepam, or antipyretics did not reduce the recurrence rate	Two meta-analyses with same results; lack of effectiveness and side effects limit the use of intermittent oral or rectal diazepam
What is the likelihood of future febrile seizures?	Synthesis of five cohort studies with risk factor analyses and a cohort study	The most important factor is the child's age; having a first degree relative with febrile or unprovoked seizures increases the risk of recurrence	Variation in risk of recurrence is related to presence of risk factors. Complex features to the seizure do not predict recurrence of febrile seizures but are associated with an increased risk of epilepsy

associated with an increased risk of unprovoked seizures. Recurrent febrile seizures and brief duration of fever before the initial febrile seizure were also risk factors. A family history of febrile seizures, temperature and age at the time of the initial febrile seizure, sex, and race were not associated with unprovoked seizures. This high quality evaluation of predictors gives an insight into the risk of epilepsy and may be used to counsel patients. However, no studies have examined the possibility of preventing epilepsy by pharmacological interventions after a first or a second febrile seizure.^{15 16} The evidence you have gathered is summarised in table 2.

Applying the evidence

From the history and the physical examination you consider this child to be at a low risk of meningitis and you decide to observe him without a lumbar puncture. After resolution of the acute episode, you reassure the parents and counsel them at a follow up visit on the risk of future seizures. For this child, the probability of frequent or potentially threatening recurrences is low. You decide that the evidence does not support using a daily anticonvulsant like phenobarbitone or sodium valproate, and that intermittent diazepam or an antipyretic agent during fever are not effective in preventing recurrence of seizures. You know you will need to spend time with the parents to help them overcome the fears and anxiety that seizures provoke and to educate them about the clinical course of febrile seizures and their consequences. You know that they may still request treatment with anticonvulsants. This will depend on the values they place on different outcomes such as risk of a subsequent seizure and the adverse effects of use of anticonvulsants. You counsel these parents that the risk of recurrence declines rapidly after six months from the previous seizure and instruct them to position the child for optimal airway patency in case of a new seizure, which is especially important in the event of vomiting. A prescription for rectal diazepam should also be given, and the parents should be instructed how to administer it in the rare event of a prolonged recurrence lasting >15 minutes.^{17 18} This approach, it has been suggested, also reduces parental fear.^{19 20}

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- Nelson KB, Ellenberg JH, eds. *Febrile seizures*. New York: Raven Press, 1981.
- Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. 1. Prevalence and recurrence in the first five years of life. *BMJ* 1985;290:1307-10.
- Joffe A, McCormick M, DeAngelis C. Which children with febrile seizures need lumbar puncture? A decision analysis approach. *Am J Dis Child* 1983;137:1153-6.
- Wears RL, Luten RC, Lyons RG. Which laboratory tests should be performed on children with apparent febrile convulsions? An analysis and review of the literature. *Pediatr Emerg Care* 1986;2:191-6.
- Offringa M, Beishuizen A, Derksen-Lubsen G, Lubsen J. Seizures and fever: Can we rule out meningitis on clinical ground alone? *Clin Pediatr* 1992;9:514-22.
- Offringa M, Hazebroek-Kampschreur AAJM, Derksen-Lubsen G. Prevalence of febrile seizures in Dutch schoolchildren. *Pediatr Perinat Epidemiol* 1991;5:181-8.
- Verburgh ME, Bruijnzeels MA, van der Wouden JC, van Suijlekom-Smit LW, van der Velden J, Hoes AW, et al. Incidence of febrile seizures in the Netherlands. *Neuroepidemiology* 1992;11:169-72.
- Newton RW. Randomised controlled trials of phenobarbitone and valproate in febrile convulsions. *Arch Dis Child* 1988;63:1189-91.
- Rantala H, Tarkka R, Uhari M. A meta-analytic review of the preventive treatment of recurrences of febrile seizures. *J Pediatr* 1997;131:922-5.
- Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures—effects on intelligence and on seizure recurrence. *N Engl J Med* 1990;332:364-9.
- Rosman NP, Colton T, Labazzo J, Gilbert PL, Gardella NB, Kaye EM, et al. A controlled trial of diazepam administered during febrile illnesses to prevent recurrence of febrile seizures. *N Engl J Med* 1993;329:79-85.
- Van Stuijvenberg M, Derksen-Lubsen G, Steyerberg EW, Habbema JD, Moll HA. Randomized, controlled trial of ibuprofen syrup administered during febrile illnesses to prevent febrile seizure recurrences. *Pediatrics* 1998;102(5):pE51.
- Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998;317:1309-12.
- Offringa M, Bossuyt PM, Lubsen J, Ellenberg JH, Nelson KB, Knudsen FU, et al. Risk factors for seizure recurrence in children with febrile seizures: a pooled analysis of individual patient data from five studies. *J Pediatr* 1994;124:574-84.
- Berg AT, Shinnar S. Unprovoked seizures in children with febrile seizures: short-term outcome. *Neurology* 1996;47:562-8.
- Freeman JM. The best medicine for febrile seizures. *N Engl J Med* 1992;327:1161-3.
- Knudsen FU. Rectal administration of diazepam in solution in the acute treatment of convulsions in infants and children. *Arch Dis Child* 1979;54:855-7.
- Dreifuss FE, Rosman NP, Cloyd JC, Pellock JM, Kuzniecky RI, Lo WD, et al. A comparison of rectal diazepam gel and placebo for acute repetitive seizures. *N Engl J Med* 1998;338:1869-75.
- Rossi LN, Rossi G, Bossi A, Cortinovis I, Brunelli G. Behaviour and confidence of parents instructed in home management of febrile seizures by rectal diazepam. *Heb Paediatr Acta* 1989;43:273-81.
- Camfield CS, Camfield PR. Febrile seizures: a Rx for parent fears and anxieties. *Contemp Pediatr* 1993;10:26-44.



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