SEIZURES ASSOCIATED WITH FEVER IN CHILDHOOD

Contributions to a rational management

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TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
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PROF. DR P.W.C. AKKERMANS M.A.
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- Offringa M, Hazebroek–Kampschreur AAJM, Derksen–Lubsen G. Prevalence of febrile seizures in Dutch schoolchildren. Paediatr Perinat Epidemiol 1991;5:181–188.
- Vink R, Offringa M, Does E van der. Management of febrile convulsions in general practice. (Het beleid van huisartsen bij convulsies bij koorts.) Huisarts Wet 1990; 33 (7): 263–7.
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To all children with seizures occurring in association with fever, and their doctors

voor Jacqueline

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Contents

1
Introduction

> Children are likely to have convulsions if the fever is high and if they are constipated, if they are wakeful, frightened, cry and change colour, turning pale, livid or red. This most commonly happens in children under the age of seven. As they grow up and reach adult years, they are no longer likely to be attacked by convulsions in the course of a fever, unless one of the most severe and worst signs appear as well, as happens in inflammation of the brain. Whether the children and the others will recover or die must be judged by the whole total of signs as described in each case. HIPPOCRATES, 400 B.C. [1]

Seizures or convulsions occur in the context of many illnesses of childhood. Hence they are common to the practice of pediatrics. A seizure is thought to occur as a result of an abnormal, sudden, excessive and disorderly electrical discharge of neurons (grey matter) that propagates down the neuronal processes (white matter) to affect an end organ in a clinically measurable fashion. Seizures are characterized by stereotyped motor activity associated with disordered perception and impaired consciousness. The particular clinical signs depend on the region of the brain in which the paroxysmal neuronal discharge occurs.

The susceptibility to (or threshold for) seizures during infancy and childhood is assumed to be related to a balance between the degree of maturation of the brain and its inherent resistance to convulse, and to the degree of immediate cerebral dysfunction from whatever cause. A seizure occurs when the functional balance is lost; the roles of maturation, genetics and environmental exposure determine whether a seizure will occur. Thus, well developed seizures are rarely seen in preterm infants, more common in full-term babies, rare again during early infancy, and very common between 6 months and 5 years of age. [2] Thereafter, the incidence of seizures declines through puberty.

A special case are seizures that occur in association with fever, because of their high frequency in young children and the related problems of management, as addressed in this thesis.

PHENOMENOLOGY

The typical attack in association with fever develops in a number of phases. It starts with a sudden loss of consciousness, accompanied by tonic muscular contractions that lead to rigid extensor posturing of arms and legs and opisthotonos. Due to contractions of the diaphragm and intercostal muscles, sometimes leading to a vocalisation or cry, the respirations cease and the child turns blue. Then, usually within a minute, rhythmic jerking of the arms, legs and head follows, often associated with vocalisations and resumption of respirations. In some cases these movements are limited to a limb or (one side of) the child's face. This clonic phase usually lasts for 5 to 10 minutes but may be longer, up to more than one hour. When it is over, the child may be drowsy, confused, crying and hard to comfort for 30 to 60 minutes. Then consciousness is regained and, depending on the cause of the attack, the child seems either without any sign of disease or manifests clinical features of the underlying causative disease. In some

cases weakness or even paralysis of facial muscles or a limb is seen. The latter may last up to several hours. After the attack's resolution, similar seizure episodes may occur during the same febrile illness.

The majority of these attacks are not witnessed by the physician and the presumption that an actual seizure has occurred is most often based only on an eye-witness account. Yet, seizures or any other paroxysmal event in children can occur with such rapidity that the observant adult may not have witnessed the entire episode. Further, recent studies show that most parents that witness their child's first seizure are extremely frightened and actually think their child is dying. [3-5] They panic and engage in all kinds of actions, except for a meticulous observation of what is happening. Thus, the eye-witness may not be able to reconstruct the action with enough accuracy to make sure that an actual seizure occurred. Unfortunately, there is no way around this reliance on the clinical history. For the clinician to decide that an actual seizure has occurred the following elements are usually required: loss of consciousness with either stiffening and myoclonic jerking or total loss of muscle tone.

FEVER, SEIZURE TYPE, DIFFERENTIAL DIAGNOSIS

Fever

An important aspect is fever, usually arbitrarily defined as a temperature ≥ 38.0° C (101.2° F). The temporal relationship between the occurrence of fever and the seizure is variable. Fever may have been present for hours or several days before the seizure, or, on the other hand, not have been noted. [6] To decide if the attack occurred in association with fever, the temperature should be taken rectally with a reliable thermometer, preferably as close in time to the seizure as possible. Seizures occurring at temperatures below 38.0° C are called non-febrile or unprovoked, and, when no underlying cause is identified, are considered idiopathic seizures. The term idiopathic (or cryptogenic) indicates that no discernible underlying disease can be found.

Seizure type

The seizure type, whether 'simple' or 'complex', is important since it relates to the probability of meningitis and the risk of later epilepsy. [7-9] Seizures are generally referred to as *simple* if they last less than 15 minutes, do not re-occur within 24 hours and are generalized, i.e., the tonic-clonic contractions involve the head, spine and all four limbs. In contrast, *complex* seizures either last for more than 15 minutes, reoccur within 24 hours, or have a partial (focal) onset, according to criteria of the International League against Epilepsy. [10]

Unfortunately, there is no gold standard for defining whether complex features were present and here the clinician has to rely again on the witness' account. Berg et al. recently found that a careful history, taken on average 23 days after a seizure, resulted in a substantially higher yield of complex features, as compared to emergency room records. [11] In another study based on a second interview with the witness and the emergency room chart, three pediatric neurologists agreed in the rating of multiple and pro-

Table 1.1. Differential diagnosis of a seizure associated with fever. [19,20]

Condition	*Usual Basis of Diagnosis*
Convulsive, acute symptomatic seizure	
CNS inflammation	HI, PE
head trauma	HI, PE
hyponatremia (dehydration, water intoxication)	HI, PE
hypoglycaemia	lab, HI
hypocalcemia	HI, PE
intoxication *	HI, workup
Nonconvulsive, neurological	
chorea-athetosis in CNS inflammation	HI, PE
movement disorder: chorea, tremor, tics	HI, PE
myoclonic syndromes	HI, PE
dystonias, hereditary or acquired	HI, PE
shuddering attacks	HI, PE
migrainous syndromes	HI
benign paroxysmal vertigo	HI, PE
parasomnias: night terrors, narcolepsy	HI
Non convulsive, non neurological	
rigor	HI, PE
tetany	HI, PE
temper tantrum	HI
reflex anoxic attack	HI
breath holding spell: pallid, cyanotic	HI
syncope: hypovolemia, anoxia, bradycardia, prolonged QT-syndrome	HI, PE
Sandifer syndrome (gastroesophageal reflux + torticollis)	
recurrent abdominal pain	HI, PE
behaviourial/psychiatric disorders: ADHD, episodic dyscontrol syndrome, pseudoseizures	HI
Febrile seizure	*exclusion of the above*
Beginning of epilepsy	*follow up*

CNS: Central nervous system; HI: history; PE: Physical examination including neurological examination.

*: Agents that may produce seizures: amphetamines, anticonvulsants when overdosed, belladonna, camphor, CO, cocaine, cyanide, cyclic antidepressants, insulin and oral hypoglycaemic agents, isoniazid, lead, lidocaine, nicotine, organophosphates, phencyclidine, phenylpropanolamine, theophylline.

longed features. [12] On the other hand, there was disagreement about focal features in 23 out of 100 seizures. [12] These results suggest that complex features may be under-reported or unrecognized during the emergency room evaluation.

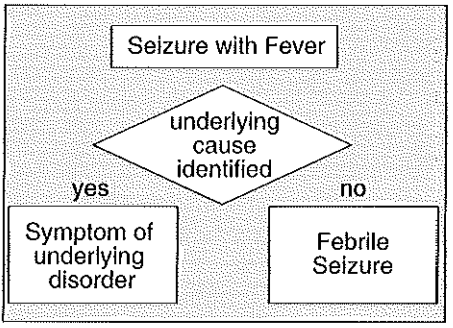
Differential diagnosis

Seizures are often described as 'symptomatic' or 'idiopathic', referring to the presence or absence of a required underlying cause. Thus, some seizures may be symptomatic of acute derangements in the central nervous system, such as anoxia, hypoglycaemia, hypocalcemia, hyponatremia, or induced by trauma, tumour, haemorrhage, infection or intoxication. Other seizures may be the result of structural abnormalities such as congenital anomalies (e.g., neurocutaneous disorders, abnormal neuronal proliferation) or glial scarring from previous episodes of anoxia or trauma.

Furthermore, many neurologic and non-neurologic conditions in children under the age of 6 years may produce a paroxysm that might be confused with seizures. Some of these can present with fever by coincidence, but most can be differentiated by the presence of a noxious precipitant, change in colour, or typical movements. The differential diagnosis of a seizure associated with fever is summarized in Table 1.1.

Febrile seizures are a special case of acute symptomatic seizures, because, apart from fever, caused by an extracranial illness, no underlying cause for the seizure can be found. The definition of febrile seizures adopted at the 1980 National Institutes of Health consensus meeting excludes children with a history of non-febrile seizures and those with an intracranial infection or another defined cause for the seizure. [13] Thus, *febrile seizure* is a diagnosis *per exclusionem* in the differential diagnosis of the clinical syndrome '*seizure associated with fever*'.

Both simple and complex febrile seizures exist. On average 20% of first febrile seizures has one or more complex features (i.e prolonged, multiple or partial). [12] Their significance for the risk of subsequent recurrent febrile seizures is investigated in this thesis.



1.1

Figure 1.1. Febrile seizure is a diagnosis per exclusionem in the differential diagnosis of the clinical syndrome 'seizure associated with fever'.

MEASURES OF SEIZURE FREQUENCY

As stated before, seizures occur in the context of many childhood illnesses. The clinician attending a pediatric emergency room (where many children with seizures are seen) needs to have insight in their underlying causes and outcomes. Since there is no animal model that can be used to study seizures with fever as they occur in infants and toddlers, any inference about the nature of this disorder has to be based on observations of patients. In search for common characteristics it is therefore imperative to use epidemiological methods.

Two main measures of seizure frequency are used in the study of seizures associated with fever, each with its specific context. **Prevalence** is the proportion of individuals within a population affected with a disease at a particular point in time. Prevalence studies are usually done by surveying medical records or interviewing selected populations to identify affected individuals at a particular point in time. For seizures with fever prevalence includes those individuals who have had at least one episode of a seizure during a febrile illness. A major determinant is the age of the study population since most seizures with fever occur between the ages of 6 months and 6 years. Prevalence is also used to describe the frequency of specific causes for the attack (such as meningitis) in a series of children that present to an emergency room. **Incidence** is the frequency measure with which new seizures develop in a population of children at risk. It presumes surveillance over a period of time and recording of new episodes. Incidence is also used in the study of recurrent seizures in children who have experienced an initial episode of a seizure associated with fever. Further discussion of the use of prevalence and incidence in this context follows in the next chapters.

CURRENT CHALLENGES IN THE MANAGEMENT OF CHILDREN WITH SEIZURES AND FEVER

Seizures associated with fever represent a heterogeneous syndrome in young children with extremely frightened parents. Although most seizures eventually appear to be benign, meningitis may present as a seizure associated with fever. Further, seizures with fever may be the first manifestation of subsequent generalized tonic clonic seizures, complex partial seizures, absence seizures and drug-resistant epilepsy.

The last sentence of the quote from Hippocrates refers to the difficult clinical management of children with seizures and fever. As today, in Hippocrates' days management consisted of providing a prognosis for the patient based on the history and the manifestations of disease at examination. In addition, the modern clinician attempts to improve this prognosis (if considered necessary), using interventions such as diagnostic tests, antibiotics and antiepileptic drugs. In doing so, he meets many challenges.

First, as he has not personally witnessed the attack, he must try to determine what has happened. As stated, many acute conditions in young children may produce a clinical picture that might be confused with a seizure. Before considering any underlying

cause, he must conjecture if in fact a seizure has occurred, and if so, if it actually has stopped.

Then, the differential diagnosis needs to be considered. Is there a need for further clinical and laboratory data, and how are these to be interpreted? For instance, the clinician must decide whether a lumbar puncture is warranted or one can safely rely on the absence of clinical signs of meningitis. At present, the need for routine investigation of cerebrospinal fluid to rule out meningitis is subject to ongoing controversy. There is no consensus on the clinical indications for a lumbar puncture. In her recent monograph, Sheila Wallace states that 'lumbar puncture is undoubtedly the most controversial acute investigation'. [14]

Next, after resolution of the acute episode, the possibility of recurrent seizures will have to be considered. In this context, the risk of frequent or severe recurrences that might carry some risk of persistent neurological damage is most relevant. Here, the clinician's role is to explain, counsel, and organize a scenario for the next seizure episode. In children considered at increased risk, prophylactic antiepileptic treatment might be started. On the other hand, the risk of just one or two uncomplicated recurrent febrile seizures would probably not justify such treatment. Thus, the decision to treat rests on a comparison of medical costs and benefits.

All these management decisions have to be made under conditions of diagnostic and prognostic uncertainty. At present, the data to back up these decisions are weak. Current pediatric textbook advice is still largely based on older insights, and invariably notes that 'there seems to be some controversy regarding the management of children with seizures and fever'. [15] Moreover, different doctors have different opinions on what should and should not be done. It is therefore not surprising that recent surveys have shown wide practice variation. [16–18]

SCOPE OF THE THESIS

Since the well known National Institutes of Health consensus conference on febrile seizures in 1980, [13] a large number of studies have addressed their pathophysiology, genetics and heredity, and the subsequent occurrence of neurological sequelae such as temporal lobe epilepsy. Recent reviews discuss risk factors for epilepsy (defined as recurrent non febrile seizures), the acute treatment of ongoing seizures, and counselling of parents. These issues will not be addressed in this thesis. Instead, the focus is on the current two main domains of uncertainty in the clinical management of children that present with seizures associated with fever: the best emergency room approach in light of the risk of an underlying central nervous system inflammation, and the child's subsequent prognosis, i.e., the probability of recurrent febrile seizures and the expectations of long term antiepileptic drug treatment to prevent these recurrences.

We carried out a series of studies. The results of these studies, reported and discussed in papers published in or submitted to international journals, form the core of this thesis.

First, two studies addressing the epidemiology of seizures associated with fever in the Netherlands were done (Chapter 2). The prevalence of seizures with fever and the steps that are taken before a child is seen at the emergency room of a hospital are investigated. The organization of the Dutch health care system, which leads to selection of children for hospital referral is highlighted.

The questions regarding emergency room management are addressed in Chapter 3. First, indicators for the presence of meningitis in children with seizures and fever are identified in a case-referent study (Section 3.1). Section 3.2 describes a prospective study designed to evaluate and extend the results of the previous study. It also offers a decision analytical approach to the core decision in the acute management: perform a routine lumbar puncture or not.

Management of recurrent febrile seizures is addressed in Chapter 4. First, a study describing the phenonemon of recurrent febrile seizures as a function of time since the first occurrence and certain risk factors is presented (Section 4.1). Then, further evaluation of the role of the child's age and the risk factors is presented in Section 4.2. Finally, a synthesis of current information is achieved in the form of a riskmodel for seizure recurrence; it's predictions are validated in a separate dataset (Section 4.3).

In Chapter 5 a general discussion of the study results is presented, followed by a concluding section in which practical guidelines for the management of children with seizures with fever are formulated.

Without exception, the studies described in this thesis were done in collaboration with other departments. All studies were designed at the Sophia Children's University Hospital and the Center for Clinical Decision Analysis at the Erasmus University in Rotterdam. The prevalence study and the investigation into the general practitioner's referral policy were done in collaboration with the School Health Care Department at the Rotterdam Municipal Health Office, and the Department of General Practice at the Erasmus University in Rotterdam, respectively. Three observational studies were carried out at the Department of Pediatrics of the Sophia Children's University Hospital in Rotterdam, the prospective study described in Section 3.2 was done in collaboration with two nearby hospitals with a pediatric emergency room, the St Juliana Children's Hospital in The Hague and the Zuiderziekenhuis in Rotterdam.

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2
Aspects of the epidemiology of seizures with fever

2.1 Prevalence of febrile seizures in Dutch schoolchildren

Martin Offringa, Alice A.J.M. Hazebroek–Kampschreur, and Gerarda Derksen–Lubsen

INTRODUCTION

Febrile seizures are one of the most common neurologic disorder of childhood, [1] and affect approximately 2% to 5% of all children in the United States and Great Britain. [2–5] Reported prevalence rates of febrile seizures in different geographic areas, however, vary from 0.1% to 15.1%. [6,7] Apart from real differences in the actual occurrence of the disorder, both differences in definition of febrile seizures and variation in study methods may have accounted for this large variation. So far, no data for the Dutch situation are available.

In 1980 the National Institutes of Health (NIH) Consensus Meeting defined a febrile seizure as ' ... an event in infancy or childhood, usually occurring between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or defined cause. Seizures with fever in children who have suffered a previous nonfebrile seizure are excluded'. [8] Virtually all studies on febrile seizures published since the Consensus Statement have adopted this definition.

The purpose of this study was to determine the prevalence of a history of febrile seizures at the age of 6 years in a well defined group of children, using a definition based on the NIH consensus statement.

METHODS

The sample size was based on the requirement that the prevalence rate of febrile seizures could be estimated with a 95% confidence interval of ± 0.5%. Assuming hypothetical prevalences of 2% and 5%, 3,000 to 7,000 subject are needed to achieve this precision, based on the standard normal approximation to the binomial distribution. [9]

In order to collect information on several thousand children, eight school physicians from the Rotterdam Municipal School Health Service participated. This public health service aims to promote and protect health, growth and development of schoolchildren through longitudinal surveillance and early detection of abnormalities. The service covers all primary schools in the Rotterdam urban and suburban area in a program of regular medical examinations. In the present study, only schools in the suburban area were

selected to participate; we made this selection because in some Rotterdam inner-city areas, up to 35% of the population is of non-Caucasian origin, and therefore is not representative of the overall Dutch population. The large suburban area of Rotterdam, however, is to be regarded as representative. In this area, all children of 6 years attend primary schools, except for approximately 1% of children who, because of psychodevelopmental retardation, attend special schools. During the study period, all suburban primary schools were visited by the 8 participating school physicians.

The data were collected between August 1989 and July 1990. Together with the invitation for the scheduled medical examination in grade 4, a questionnaire was mailed to all parents one week before the visit to the school physician. They were asked whether their child had ever experienced '... an attack of loss of consciousness with or without jerking of the body—a sort of 'epileptic' attack—during a period of fever'. In addition, it was asked if any of the sibs or parents of the child had ever experienced such an attack in their childhood.

At the visit to the school physician, the questionnaire was taken in by a nurse, who filled out the child's date of birth, gender and ethnic group, and checked it for completeness and errors. In the event that the parents responded positively about potential febrile seizures or had experienced any difficulty in filling out the form, the school physician reviewed the form with the parents. If a febrile seizure was considered to have

Table 2.1.1. Prevalence of a history of febrile seizures (FS) by gender, family history and ethnic group.

Feature	*Total (n = 3,570) No.*	*Prevalence of FS (n = 140) No. (%)*	*Rate Ratio* (95% CI)*
Gender			
male	1,835	71 (3.9)	1.0 (0.8–1.2)
female	1,735	69 (4.0)	1.0‡
First degree family history of FS†			
positive	193	30 (15.5)	4.5 (3.2–6.4)
negative	3,333	110 (3.3)	1.0‡
Ethnic Group			
non Caucasian	351	18 (5.1)	1.3 (0.9–2.0)
Caucasian	3,219	122 (3.8)	1.0‡

*Rate Ratio calculated for index category compared to reference category with test-based 95 % confidence interval (CI).
† In 44 instances of uncertain history, subjects were excluded from this analysis.
‡ Reference category.

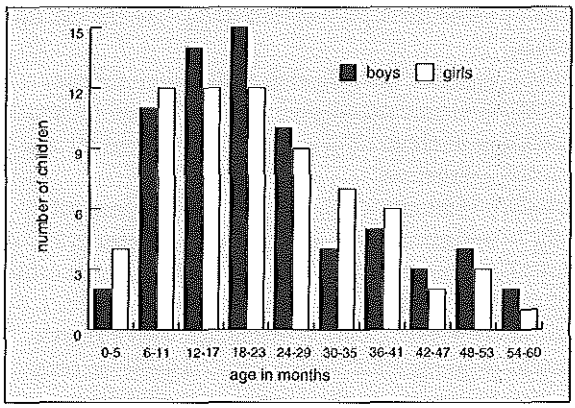
occurred, the school physician collected information on the age at onset, recurrent seizures, hospitalization, medication used and discharge diagnosis. Based on this information, the school physician made a final decision on whether any reported attack met the criteria for febrile seizures mentioned before. When in doubt, parental consent was requested in order to collect additional information from the family physician or the pediatrician involved.

Prevalence rates and their 95% confidence intervals were calculated under the assumption of a standard normal approximation to the binomial distribution; [9] for different categories of children at risk of febrile seizures, prevalence rate ratios and their test based 95% confidence intervals were calculated. [10]

RESULTS

A total of 3,649 children were invited for the routine medical examination. Information on the occurrence of febrile seizures was available for 3,570 children (98%); 79 did not respond to the invitation for the scheduled examination. Median age at the time of the visit to the school physician was 6.0 years (range 5.6 to 8.2). The percentage of boys was 51.4%; ethnic groups were, Caucasian 87.0%, Caribbean or Surinam 3.4%, Turkish or Moroccan 0.7%, and mixed 6.9%.

Of the 3,570 investigated children, 140 (3.9%, 95% confidence interval 3.3% to 4.5%) were considered to have experienced at least one febrile seizure. Median age at onset was 18.2 months (range 3 to 70); for boys, 17.1 months and, for girls, 19.5 months (see Figure 2.1.1). Sixty-nine percent experienced their first seizure between 6 and 36 months of age. The prevalence of a history of febrile seizures by gender, family history and ethnic group is given in Table 2.1.1. No difference in prevalence rate between boys and girls was found (rate ratio 1.0; 95% confidence interval 0.8 to 1.2). A family history could not be obtained in 44 out of the 3,570 investigated children (1.2%). Among the 193 who had a positive first-degree family history of febrile seizures, the prevalence rate was 15.5%, and among the 3,333 with a negative family history 3.3% (rate ratio 4.5; 95% confidence interval 3.2 to 6.4). Non-Caucasians had a slightly higher prevalence of febrile seizures then Caucasians (rate ratio 1.3; 95% confidence interval 0.9 to 2.0). There were no differences between children with and without febrile seizures in month of birth.



2.1.1

Figure 2.1.1. Age at onset in months, by gender.

Recurrent seizures during the same febrile illness occurred in 19 (14%). During the average follow-up period of 4.3 years from the initial seizure (range 3.2 to 5.5 years), 36 (26%) children suffered seizures in subsequent febrile episodes. In these children, the time lapses between the initial febrile seizure and the first recurrence ranged from 1 to 24 months (median 2 months); 82% of the first recurrent seizures occurred within 2 years after the initial seizure. Eleven children were reported to have experienced three or more recurrent seizures.

Of all children with at least one febrile seizure, 35% reported to have visited the emergency room of a hospital directly after the first seizure; the rest had been managed at home by the general practitioner. Ten children had used anticonvulsant medication for at least 6 months, six of them after a recurrent seizure.

DISCUSSION

To determine the risk of febrile seizures in a given population, two approaches can be considered: (1) a cumulative incidence study of a cohort of life birth and (2) a prevalence survey among subjects at an age beyond the typical risk age. In previous studies on the occurrence of febrile seizures, both the cohort cumulative incidence approach [2,3] and the prevalence survey approach [4,5] have been adopted.

The present study represents a cross-sectional prevalence survey of a history of febrile seizures in children who have reached the age of primary school and are free of major neurologic impairment. Since children who do not reach the age of primary school or suffer from persistent developmental impairment are not represented, the prevalence rates reported here underestimate the risk of febrile seizures up to primary school age, expressed as the percentage of live births who experience febrile seizures before that age. However, since large studies of cohorts followed from birth have demonstrated that febrile seizures in and of themselves do not appear to lead to increased mortality—either acutely or on a long-term basis—[2,3,11] and since the incidence of severe neurological sequelae subsequent to febrile seizures is extremely low, [3,12] we believe that the difference between prevalence at primary school age and the risk up to that age is only of minor magnitude.

In a review of the literature, Tsuboi suggested the following explanations for the large difference in reported rates of febrile seizure prevalence: [13] (1) the use of different definitions of febrile seizures, (2) different methods of case ascertainment, and (3) true differences in prevalence rates between populations.

Most of the surveys conducted before 1980 provide figures not readily comparable to the results from the present study. Investigators sometimes included all seizures occurring with febrile illness, or any idiopathic seizure associated with fever, while others on the other hand included only 'simple' (generalized, short and single) febrile seizures. In only a few instances special attention was given to children with a known prior neurological abnormality. Results from the cited studies [2–5] are suitable for comparison with the results from the present study, for in these studies the same definition of febrile seizures was used, all seizure types were included and cases with intracranial

infection were excluded. Also, children with a prior neurological abnormality were described separately.

A second source of variation in prevalence rates in the various studies is the procedure and completeness of case ascertainment. Children under the age of 6 years are prone to a number of different sorts of attacks (such as breath holding, rigor and syncope) that might be confused with febrile seizures. In order to avoid over- and under-reporting in a survey, it is therefore crucial to take an adequate and detailed history of any reported attack. Methods used in previous studies have included case finding in medical records, [2] questionnaire surveys, [4] and visits by health care workers to members of an entire birth cohort. [5] As has been stated by Tsuboi, [14] perhaps the most reliable method is ascertainment by clinical examination of all subjects to be investigated by a physician. We believe that the strategy used in the present study comes closest to this ideal.

A history of febrile seizures was found in 3.9% of the children. Studies conducted in the United States and Great Britain have reported prevalence rates range from 2.3% to 4.2%. [2–5] Rates as high as 7.9% and 15.1% were found in Japan and in some populations in the Pacific, [7,13] which, as Tsuboi suggested, [13] may be due to the closer living arrangements among family members in these areas, which makes parental detection of seizures more likely. Ethnic groups represented in this study reflect the current overall ethnic composition of the Dutch population. On 1 January 1989, the distribution of these ethnic groups was: Caucasian 93.3%, Caribbean or Surinam 1.9%, Turkish or Moroccan 2.1%, and mixed 2.2%, respectively (n = 14,805,240). [15]

The median age at onset in the present study was 18 months, and 69% of the children had their first seizure between 6 and 36 months of age: this finding is in close agreement with findings in all cited studies. No relation was found between month of birth and the prevalence of febrile seizures; this is in accordance with Tsuboi's report. [16]

As observed in most other studies, [3–5] there were no differences in prevalence rate between boys and girls (Table 2.1.1): in some studies slightly higher rates have been found for boys. [2,12,13] No gross difference between boys and girls was found in age at onset (Figure 2.1.1). A more than four-fold increase in risk existed in children with a first-degree family history of febrile seizures (Table 2.1.1). This higher vulnerability has recently been demonstrated in two other studies. [17,18] In the present study, no correction was made for the number of sibs, a factor that might well influence the magnitude of the estimated effect, especially in large families. A moderate increase in risk for febrile seizures was found for non-Caucasian children (Table 2.1.1), but the difference did not reach statistical significance at the p=.05 level.

In the present study, 14% of the children with febrile seizures were reported to have suffered a multiple initial seizure. In only one population-based study the occurrence of multiple seizures at the first febrile seizure was reported as a separate feature in 15% of the children; [19] most other studies consider combinations of focal, prolonged (usually 15 minutes) and multiple seizures as 'complex' seizures, to be contrasted to 'simple' febrile seizures, and report rates of 18% to 25%. [20]

Cumulative incidence studies have shown that of all recurrent seizures in subsequent febrile episodes 90% may be expected to occur within 2 years after the initial febrile seizure. [2,3] In the present study, recurrent seizures occurred in 26% during an average follow up time of 4.3 years; four of the 140 children were treated with anti-epileptic medication after their first seizure. Other population based studies have reported recurrence rates ranging from 25% to 48%, with an average of 33%. [2–5,12,19]

Not all children with a first febrile seizure are referred to a hospital. Their number depends largely on the organization of the health care system, and the availability of immediate care by general practitioners. Two studies conducted in Great Britain—which has a health care organization similar to the Dutch system—reported that 39% to 55% of children with a first febrile seizure were treated entirely at home by their general practitioner. [4,5] In a recent questionnaire survey among general practitioners in the urban and suburban area of Rotterdam, the participating 202 general practitioners reported to have managed on average 56% of first febrile seizures at home. [21] In the present study, only one third of the children reported to have visited the hospital, either after referral by their general practitioner or after self-referral.

CONCLUSIONS

In conclusion, we believe the reported estimate of febrile seizure prevalence of 3.9% is fairly accurate for The Netherlands, and is in accordance with rates from recent studies with similar qualitative features conducted in the United States and Great Britain.

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2.2 Management by general practitioners, and referral

INTRODUCTION

Seizures associated with fever affect 3% to 5% of all children. [1–3] In some cases a seizure will be the first sign of an intracranial infection or a metabolic dysregulation. Yet, in most instances no underlying cause will be detected: the child has suffered a 'febrile seizure'. [4]

In the Netherlands, not all children with seizures associated with fever are seen in a hospital. The Dutch health care system distinguishes between so called primary care (general practice) and secondary (hospital) care. Any patient will first contact the general practitioner (GP), regardless of the problem. In a case of emergency, the GP will pay a home visit and, if considered necessary, arrange (ambulance) referral to hospital. Thus, the GP plays a crucial role in selecting children for referral, since he is most often the first one to be consulted by the parents. As a result, children seen in the emergency room of the hospital after a seizure with fever constitute a selected group. It is noted that self-referral occurs also, since the emergency rooms of hospitals will not turn away children who come directly without clinical evaluation.

To gain more insight in the selection process in primary care, we conducted a study among all GPs who refer patients to hospitals in the Rotterdam urban and suburban area. The aim of the study was to determine a) how often the GP sees children that suffer seizures associated with fever, b) which proportion of these children visits the hospital, and c) on which basis the GP refers.

METHODS

A questionnaire was sent to all 316 GPs in the Rotterdam urban and suburban area. Data from the local General Practitioners Association were used to complete the mailing list.

A seizure associated with fever was defined as an attack of loss of conscience, associated with general or focal jerking of the body, at a temperature of at least 38.5 degrees Celsius. Here we defined the clinical problem *seizure with fever*, as opposed to the final diagnosis of *febrile seizure*, that is established after all possible causes of the insult have

Table 2.2.1. Referral policy in three situations: (1) seizure shorter than 15 minutes and ceased at the time of the general practitioner-patient contact, (2) seizure longer than 15 minutes and ceased, (3) seizure longer than 15 minutes and ongoing.

situation	*referral*		
	never (%)	*sometimes (%)*	*always (%)*
seizure < 15 min, ceased (n = 194)*	42	49	9
seizure > 15 min, ceased (n = 197)†	2	52	46
seizure > 15 min, ongoing (n = 197)†	1	19	80

* Not reported by 4 respondents † Not reported by 1 respondent

been excluded. [4] We distinguished seizures with a duration shorter or longer than 15 minutes. In a multiple choice format the GPs were asked whether the timing of the seizure in the course of the febrile illness or the height of the temperature was of relevance for the decision to refer. Also, specific reasons for referral after a first attack and after a recurrent episode were offered. We asked if the GP would give advise to the parents by telephone before his emergency visit directly after the attack. At several questions the respondents could add comments.

Two weeks after the questionnaires were sent the GPs were approached by telephone to remind them of the study. Three weeks later a written reminder was sent by mail.

RESULTS

Of the 316 GPs 202 (64%) responded; four of the 202 returned questionnaires were not filled out. The 198 remaining respondents reportedly provided health care for a population of 455,600 people; this means on average 2,301 per practice. According to data from the Municipal Registries a total of 729,197 people lived in the Rotterdam urban and suburban area on January 1, 1988. Of these, 6.3 percent were in the ages between 0.5 and 5 years. The average practice of all 198 participating GPs would thus contain 145 children in the age group at risk for febrile seizures.

The 198 GPs reported that they were confronted on average 2.3 times per year with a child suffering a seizure associated with fever (range 0-10). In 66% of the cases these were the child's first attack; in one out of three it was a recurrence after an earlier episode. On average 44% of all patients was seen in the hospital, either after the GP's home visit or by self-referral. Ninety-six percent of the participant GPs stated that par-

Table 2.2.2. The six most common referral policies.

seizure < 15 min ceased	*seizure > 15 min ceased*	*seizure >15 min ongoing*	*% of GPs (n = 198)*
sometimes	always	always	27
never	sometimes	always	19
sometimes	sometimes	always	15
never	sometimes	sometimes	10
never	always	always	9
always	always	always	9

ents should first contact their GP in the event of a seizure associated with fever; only 2 respondents thought that it might be better to directly visit the hospital.

Table 2.2.1 shows the reported referral policy in 3 distinct situations with regard to seizure duration. Of the 81 GPs who reported 'never' to refer a child after a febrile seizure <15 minutes, 28% reported to 'always' refer a child that had experienced a seizure of longer duration. Of the 96 GPs that would 'sometimes' refer a child with a short seizure, half would 'always' refer after a longer attack. Only 3 GPs reported to 'never' refer a child after a seizure of 15 minutes or longer, provided the attack had terminated on the GP's arrival.

The six most common referral policies with increasing seizure duration are shown in Table 2.2.2. The category 'never' occurs 3 times, always in cases of short attacks. This strategy is reported by 75 GPs, and is probably based on their experience that such attacks are rarely associated with an intracranial infection or other threatening condition. The category 'refer always' occurs mostly in the columns of seizures longer than 15 minutes. Only 20 physicians (10%) never used the word 'always'; apparently they adjust their decision to refer on individual patient characteristics.

Most respondents (74%) indicated that the timing of the seizure in the course of the febrile illness would be of influence. Half of them indicated that a benign febrile seizure occurs in the beginning of the febrile illness, when the temperature is rising. The actual height of the temperature after the seizure was of less influence; about one out of three respondent considered this important. In these all instances, they would refer the child if a relative low temperature was found.

The answers to the multiple choice questions about the indications for referral after either a first attack or a recurrence are summarized in Table 2.2.3. More than half suggested further analysis by a specialist after a recurrent episode of seizure associated with

Table 2.2.3. Reasons to refer a child with a first or a recurrent seizure with fever < 15 minutes.

Reason	*first occurrence* % *GPs*	*recurrence* % *GPs*
Any child with a first or recurrent seizure with fever needs further analysis	18	64
An intracranial process cannot be excluded at home	16	17
The probability of a second seizure is increased and a specialist needs to consider prophylactic drugs	10	-
Parental anxiety	18	9

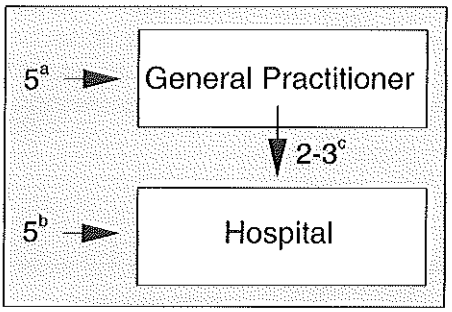
fever. Seventy-eight percent of the respondents reported to give advises by telephone before actually visiting the child at home. These advises included: 'try to lower the child's temperature (undress, cool water)' (38%), 'keep the airway free' (27%), 'try to prevent self-wounding' (18%), 'administer an antipyretic' (18%) and 'stay calm' (18%).

DISCUSSION

Frequency of seizures with fever

The results of this study indicate that a GP with an average practice size in Rotterdam is confronted on average 2.3 times per year with a child with a seizure associated with fever. Of these, two out of three are first occurrences. If the average practice reflects the age composition of the general population and comprises 6.3% of children within the risk ages of 0.5-5 years, this means that in the Rotterdam urban and suburban area each year 10 children per 1,000 will experience their fist seizure associated with fever. Based on this yearly incidence, a cumulative incidence of 4.4% at the age of 6 years can be calculated. This figure is in agreement with the prevalence of febrile seizures found in Section 2.1.

In another recent Dutch study, 6,195 children between the ages of 3 and 72 months were followed during one year in 161 general practices throughout the country. [5] Thirty episodes of a first seizure associated with fever were observed. Based on these data, an overall incidence rate of 4.8 per 1,000 child-years was calculated (95% confidence interval 3.1 - 6.6/1,000 child-years). [5] Contrary to the present study, only contacts with the GP were recorded: children that were seen in a hospital after self-referral



2.2.1

Figure 2.2.1. Occurrence of first seizures associated with fever per 1,000 child-years at risk (ages 0.5 to 5 years), according to the place where they are first seen. Estimates based on a) this Chapter, b) this Chapter and Section 3.2, c) this Chapter and Reference 5.

were not included. The difference in incidence (10 versus 4.8/1,000 child-years) may therefore be due to those patients that choose to directly visit a nearby hospital without consulting their GP in advance.

In population-based studies recurrent febrile seizures occur in 30 to 40%. [6] In the present study one out of three episodes was reported to be a recurrent seizure. It follows that in the Rotterdam area each year on average 5 per 1,000 children experience a recurrent seizure.

Hospital visits

The participating GPs in this study indicated that they would treat more than half of the seizures at home. Ross et al. found in a study among 16,000 children that 55% of 366 children with febrile seizures was managed at home. [7] In the study by Verity et al. 39% was reported to have been treated at home. [2] We conclude that marked selection occurs in the primary care setting. On the other hand, in an urban setting such as Rotterdam, many parents choose to directly visit the nearest hospital emergency room. In a consecutive series of 365 children with seizures associated with fever that visited the emergency rooms of three urban hospitals, only 142 (39%) were referred by their GP (Section 3.2). Given the results of the quoted Dutch study and the present study, patient flow as presented in Figure 2.2.1 may be conjectured.

Referral policy

Of all seizures with fever, 7-13% are reported to last longer than 15 minutes. [6] Half of the respondents in our study would 'always' refer children with such an attack. In the event of an ongoing seizure longer than 15 minutes, 80% would always refer. On the other hand, when the seizure is short, 9% reported to refer. Given these results, one might expect that most children that present with long duration in the hospital emergency room will have been referred by a GP. This actually appears to be the case (See Section 3.2).

Although old teaching dictates that febrile seizures occur in the beginning of the febrile illness, it is not uncommon that an attack occurs on the second or third day, especially when antipyretic drugs have been used. [8] There is evidence that seizures

occurring after several days of febrile illness carry a higher risk of meningitis. [9,10] In the present survey three out of four of the respondents indicated that the timing of the seizure in the course of the illness is related to its nature (i.e., either benign or symptomatic of some underlying disease), and that seizures on the first day would probably be benign.

CONCLUSIONS

We conclude that about 50% of children with seizures and fever seen by the GP in the Netherlands is treated at home. He will select those children for referral that have seizures of long duration or a recurrent episode. A yet important fraction of children seen in the hospital are self referred cases.

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3
Acute management

3.1 Seizures and fever—Can we rule out meningitis on clinical ground alone?

Martin Offringa, Auke Beishuizen, Gerarda Derksen–Lubsen, and Jacobus Lubsen

INTRODUCTION

A major concern in a young child presenting with fever and a seizure is that the child might have meningitis. There is no question that, compared with the presence of fever alone, a seizure associated with fever carries a higher likelihood that the child has meningitis. However, there is no consensus on the clinical indication for performing a lumbar puncture, and the question of whether cerebrospinal fluid examination is warranted in all children with a first seizure associated with fever remains unresolved.

Several case reports in the past two decades indicated that meningitis had occurred in young children who presented initially with a clinical picture quite similar to benign febrile seizures. [1–3] Recognizing that young children may occasionally lack specific physical signs of meningitis and that in the postictal phase the neurologic examination of these children may not be reliable, the authors of these studies recommended that lumbar puncture be routinely performed in all children with a first episode of seizures associated with fever. Other investigators, however, have questioned the necessity of routine lumbar puncture, and it has been repeatedly suggested that clinical information be used to select children at high risk for meningitis. [4–7]

To our knowledge there has been only one reported attempt to evaluate combinations of specific symptoms and signs that might clinically identify children with meningitis among all those with seizures associated with fever (or inversely, identify those for whom lumbar puncture is unnecessary). In a retrospective study, Joffe et al described five factors from the history and physical examination that identified all 13 children whose seizures were secondary to meningitis in a group of 241 children with seizures associated with fever. [6] When used in combination, these risk factors would have spared 137 children (62%) who did not have meningitis the lumbar puncture procedure. These risk factors included: 1) a physician visit within 48 hours before the seizure; 2) the occurrence of seizure(s) at the emergency room; 3) focal seizures; (4) suspicious findings on physical examination (i.e., petechiae and signs of circulatory failure); (5) abnormal neurological findings on physical examination (i.e., signs of meningeal irritation and various degrees of coma). The authors recommeded that their findings be confirmed and expanded in other patient groups.

Since the publication of the study by Joffe et al, there have been no other reports on the diagnostic usefulness of these specific clinical indicators. [6] The purpose of the present study is to determine to what extent information readily obtainable from a history and physical examination in these children can serve as tools in assessing the likelihood of meningitis and to evaluate the 'risk factors' as postulated in the previous study mentioned above.

METHODS

Between March 1985 and March 1987, 309 children between 3 months and 6 years of age with a first episode of a seizure associated with fever were seen consecutively at the emergency room of two urban hospitals in the western part of the Netherlands (Sophia Children's Hospital in Rotterdam and Juliana Children's Hospital in The Hague). At both sites, patients were identified through a review of emergency-room records and a search of the hospital information system for diagnostic codes of 'seizure and fever', 'meningitis', 'encephalitis' and 'febrile seizures'.

The final diagnosis (i.e., meningitis or no meningitis) was determined for all these children by review of the charts, which are standardized, problem-oriented case records in both hospitals. If a lumbar puncture had been performed, a positive (bacterial or viral) culture of the cerebrospinal fluid or cerebrospinal fluid-pleocytosis of at least 10 white blood cells /cu mm were considered proof of meningitis. This relatively low cut-off level was chosen because in the context of seizures any pleocytosis above this level would prompt the clinician to initiate empirical treatment for suspected meningitis. If a lumbar puncture had not been performed, the final diagnosis was based on the clinical course during subsequent observation or on re-evaluation within 24 hours in the emergency room.

Among the 309 patients with a first seizure associated with fever, 23 cases of meningitis were detected. These represent the cases in the present study. From the remaining 286 children, 69 patients without meningitis were selected with the use of a table of random numbers. These form the referent group. A case:referent ratio of 1:3 was used because, compared with a study design with a 1:1 case:referent ratio, greater precision is achieved in the assessment of the relationship between clinical indicators and the presence of meningitis, while expanding the case-referent ratio beyond 1:3 will not lead to a substantial increase in precision. [8]

The charts of the 92 patients (the 23 cases of meningitis and 69 referents) were reviewed, and data regarding preselected items of history, physical examination and laboratory results were abstracted. The selection of variables was based on on clinical experience ans also on the suggestion in previous studies that these items might discriminate between patients with and without meningitis. [6,9,10]

The relationship between a clinical indicator and the presence of meningitis was assessed by calculating odds ratios from a 2×2 table which relates the presence or absence of the indicator to the outcome (i.e., meningitis cases or referents). [11] An odds ratio of 1 for a particular item indicates no association, and an odds ratio higher than 1

indicates an increased probability of meningitis if the indicator is present. The 95% confidence intervals were calculated according to Taylor. [11]

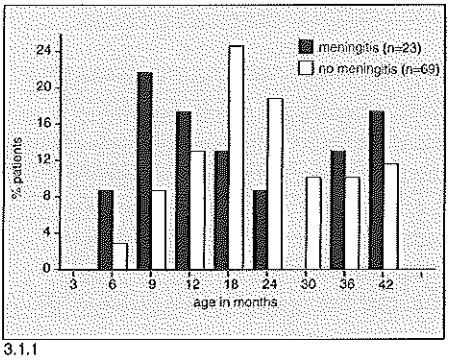
Sensitivity and specificity of clinical indicators were obtained from the cases and the referents respectively; 95% confidence limits for these sensitivities and specificities were calculated using the exact method. [12]

The (posterior) probability of meningitis, given the presence or absence of a clinical indicator, was assessed through calculation of likelihood ratios for the presence (LR+) and absence of that indicator (LR-) and their 95% confidence intervals (see Appendix A). Based on these likelihood ratios, the posterior meningitis probabilities were determined using Bayes' rule. [13] To this end, the prior probability of meningitis was taken as 7%, the observed prevalence rate of meningitis in this consecutive series.

RESULTS

The median age at presentation of all 309 patients with a first seizure associated with fever was 18.4 months (range: 3 to 52 months); 54% were boys. Of all children, 171 (65%) underwent lumbar puncture. None of the children with a cerebrospinal fluid white blood cell count lower than 10 /cu mm was initially treated for meningitis. In all 138 children (45%) who did not undergo lumbar puncture, meningitis could be excluded on clinical ground at re-evaluation. Among the 286 children without meningitis, no other known cause of the seizure (e.g., metabolic) was found. They were considered to have suffered a 'febrile seizure'.

All of the 23 children with meningitis underwent lumbar puncture at first evaluation and clinically developed meningitis. In 18 of these children, cerebrospinal fluid cultures revealed the cause of the infection: 16 were bacterial (*H. influenzae*: 10; *Str. pneumoniae*: 3; *N. meningitidis*: 2; *M. tuberculosa*: 1) and 2 were viral cases of meningitis (enterovirus: 1; mumps: 1). Four of the five remaining children with meningitis (more than 10 white blood cells /cu mm in the cerebrospinal fluid) had been treated with antimicrobial agents prior to the seizure; in the fifth case the culture remained sterile, without a proper explanation.



3.1.1

Figure 3.1.1. Age at first seizure associated with fever; percentage with and without meningitis.

Ninety-two children were further studied (23 cases and 69 referents). The age distributions are shown in Figure 3.1.1. An unimodal age distribution was observed for children without meningitis; no great age differences were found for children with meningitis. Of the latter, 11 out of 23 children with meningitis were under the age of 1 year; 7 were older than 2.5 years.

Results of routine blood tests done on admission at the emergency room (such as peripheral total white blood cells and

serum sodium concentration) did not discriminate between children with or without meningitis, except for the erythrocyte sedimentation rate: an elevated sedimentation rate was found in 61% of the children with meningitis and in 26% in children without the disease (χ^2, $p < .05$).

Clinical characteristics and their association with meningitis are shown in Table 3.1.1. They are divided into four categories: complex features of the seizure, features from the history of the present febrile illness, classic (so called 'Major') signs of meningitis, and other suspicious signs from the physical examination that might be indicative of meningitis (so called 'Minor', but not less important signs). A higher proportion of boys was observed in the meningitis group (odds ratio: 3.3, 95% confidence interval 1.2 to 9.3), as were seizures with a duration > 15 minutes (odds ratio: 9.8; 2.8 to 33.6) and multiple seizures (odds ratio: 2.8; 1.0 to 7.6). Children with meningitis had more often visited a general practitioner during the 48 hours before the seizure (odds ratio: 3.1; 1.1 to 8.5), and were significantly more likely to have been vomiting or drowsy before the seizure (odds ratio: 3.9; 1.4 to 10.9; and 7.1; 1.9 to 27.3, respectively). At the time of the physical and neurological examination the classic ('Major') signs of meningitis (petechiae, definite nuchal rigidity, coma) occured only in children with meningitis. After exclusion of all children with one of the classic signs, dubious nuchal rigidity was observed in two of the remaining seven meningitis cases and in six of the 69 referents. Convulsions and paresis or paralysis on examination in the emergency room were observed significantly more often among children whose seizure was secondary to meningitis (odds ratio for both: 4.6, 1.4 to 14.6).

The discriminating ability of indicators is shown in Table 3.1.2. The presence of petechiae, nuchal rigidity, and or 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 meningitis probability 100% (95% confidence interval 31 to 100%). Other characteristics (complex features, history features, 'Minor' signs) had a lower LR+ and therefore yielded a lower posterior meningitis probability. On the other hand, all indicators had low likelihood ratios when they were absent (LR-, Table 3.1.2), resulting in very low meningitis probabilities given the absence of these indicators.

In Table 3.1.3, sensitivity and specificity are given of the 'risk factors' proposed by Joffe et al. (a physicians visit within 48 hours before the seizure; the occurrence of seizure(s) in the emergency room; focal seizures; suspicious findings on physical examination, such as petechiae and or signs of circulatory failure; and abnormal neurologic findings on physical examination such as signs of meningeal irritation and various degrees of coma). [6] Also, a comparison with the performance of these items in Joffe's own study is presented. Except for 'abnormal neurological findings' the 95% confidence intervals for sensitivity and specificity obtained from our series cover the results of Joffe et al (Table 3.1.3). [6]

Table 3.1.1. Distribution of clinical indicators of meningitis among cases and referents.

Indicator	*Meningitis Cases (n = 23)* No. (%)	*Referents (n = 69)* No.(%)	*Odds Ratio*	*95% CI*
Gender				
male	17 (74)	32 (46)	3.3	1.2–9.3
Complex features of seizure				
Focal seizure	5 (22)	9 (13)	1.9	0.6–6.6
Duration > 15 min	10 (43)	5 (7)	9.8	2.8–33.6
Multiple seizure	10 (43)	15 (22)	2.8	1.0–7.6
At least one complex feature	17 (74)	26 (38)	4.6	1.6–13.4
History features				
At least 3 days ill	10 (43)	21 (30)	1.8	0.7–4.6
Seen by GP* in prev. 48 Hrs	9 (39)	12 (17)	3.1	1.1–8.7
Drowsiness at home	7 (30)	4 (6)	7.1	1.9–27.3
Vomiting at home	11 (48)	13 (19)	3.9	1.4–10.9
At least one history feature	18 (78)	32 (46)	4.2	1.4–12.5
Physical signs				
I 'Major' signs				
Petechiae	3 (13)	0 (0)	23.7	1.2–478†
Nuchal rigidity, definite	11 (48)	0 (0)	128	7.1–2,311†
Coma	6 (26)	0 (0)	52	2.7–960†
At least one 'Major'sign	16 (70)	0 (0)	305	17–2,500†
II 'Minor' signs				
Nuchal rigidity, dubious	2 (9)	6 (9)	2.1	0.4–11.9‡
Drowsiness	12 (52)	18 (26)	6.8	2.1–22.0§
Convulsing on examination	7 (30)	6 (9)	4.6	1.4–14.6
Paresis or paralysis on examination	7 (30)	6 (9)	4.6	1.4–14.6
At least one 'Minor' sign	21 (91)	24 (35)	19.7	4.3–91.1

* GP: general practitioner or family doctor;
† Odds Ratio and 95% Confidence Interval determined after adding a value of 0.5 in each cell of tables containing a 0 count [23];
‡ Odds Ratio determined after exclusion of children with definite nuchal rigidity;
§ Odds Ratio determined after exclusion of children with coma.

Table 3.1.2. Discriminating ability of combinations of clinical indicators. Likelihood ratios and meningitis probabilities with 95% confidence interval (95%CI) for the presence and absence of combinations.

*Combination of indicators**	*Cases (n = 23)*		*Referents (n = 69)*	
	No.	*(%)*	*No.*	*(%)*
At least one complex feature	17	(74)	26	(38)
At least one history feature	18	(78)	32	(46)
Either a complex or a history feature	23	(100)	45	(65)
At least one 'Major'sign	16	(70)	0	(0)
At least one 'Minor' sign, after exclusion of children with any 'Major' signs	5 /7	(71)	24	(35)

* See Table 1 for categories; NOTE This should read as clinical characteritics.
[1] p(MII+): posterior probability of meningitis when indicator present; p(MII-) posterior probability of meningitis when indicator absent; Calculated for meningitis prevalence of 7%.

Table 3.1.3. Sensitivity and specificity (95%CI) of items proposed by Joffe et al. [6] in the present study.

Item	*Sensitivity*	*Se-Joffe*	*Specificity*	*Sp-Joffe*
Physician's visit	0.39 (0.20–0.62)	[0.46]	0.83 (0.72–0.91)	[0.84]
Seizure in emergency room	0.30 (0.13–0.53)	[0.23]	0.91 (0.82–0.97)	[0.96]
Focal seizure	0.22 (0.08–0.44)	[0.38]	0.87 (0.77–0.94)	[0.91]
Suspicious physical findings	0.13 (0.03–0.34)	[0.23]	1.00 (0.96–1.00)	[0.97]
Abnormal neurologic findings	0.65 (0.43–0.84)	[0.92]	0.91 (0.82–0.97)	[0.84]

LR- (95%CI)	*LR+ (95%CI)*	*p(MI+)[f] %*	*p(MI-)[f] %*
0.42 (0.21–0.85)	1.96 (1.33–2.89)	13 (9–18)	3 (2–6)
0.41 (0.18–0.91)	1.69 (1.21–2.35)	11 (8–15)	3 (1–6)
0 (0–1.0)	1.53 (1.29–1.82)	10 (9–12)	0 (0–7)
0.30 (0.16–0.57)	∞ (6.0–∞)	100 (31–100)	2 (1–4)
0.44 (0.13–1.43)	2.05 (1.16–3.63)	13 (8–21)	3 (1–14)

DISCUSSION

Many authors have given their recommendations on the use of lumbar punctures after a seizure associated with fever. These recommendations range from doing routine lumbar punctures in all such children, [14,15] to doing them only in children under three years of age, [2] and from children over three 3 and under 2 years, [16] to only when the seizure associated with fever presents before the age of 18 months. [4,7,17] In contrast, considering the uneventful recovery in a study of 148 children who did not have lumbar punctures and the inconvenience and possible dangers of routine lumbar puncture in children at low risk for meningitis, Lorber et al. state that lumbar puncture should not be a routine investigation but should be done only 'on indication'. [5]

It is, therefore, not surprising that clinical practice varies markedly, as shown in a study by Asnes and co-workers. [18] In 1985 Chessare et al. again illustrated this variation in management. [19] They presented, by questionnaire, a typical case of a simple febrile seizure in a previously healthy 2-year-old-boy to 584 physicians who referred children to the Children's Hospital in Boston; 48% of the 336 respondents said they would perform lumbar puncture on this boy, 37% wouldn't, and 15% was not sure. No differences in management preferences were found between pediatricians and other physicians.

Given these varying recommendations and different approaches to a single case, one must assume that making the decision to perform a lumbar puncture in an individual

child is complex, and is influenced by many factors. One of these factors certainly is the perceived probability of meningitis in a child with a seizure associated with fever.

Among all children with seizures associated with fever the prevalence of meningitis is low. Recently, Wears et al. reviewed seven studies performed in urban hospital emergency rooms and found, among 2,100 cases of seizures associated with fever, an overall meningitis prevalence of 1.2%. [20] Several investigators have found figures ranging from 3% to 5%. [5,6] In the present clinical study, 7% of the children who visited the emergency room of the two hospitals with a first seizure associated with fever had seizures secondary to meningitis.

The above figures indicate that a large number of 'unnecessary' lumbar punctures would be done if one were to perform a lumbar puncture in all children with a seizure associated with fever. The present study was therefore designed 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. Furthermore, our aim was to verify the findings of an earlier study.

In our study, meningitis occurred at all ages, with an slight preponderance in the lowest and highest age groups (Figure 3.1.1); 78% were under the age of 12 months or older than 2.5 years. Blood-test results at first evaluation showed more abnormal erythrocyte sedimentation rates in the meningitis group; it takes, however, at least one hour before results from this test become available. The white blood cell count or serum sodium concentration appeared not to be informative. The lack of usefulness of these laboratory tests has been reported previously. [4,15,17] We conclude that neither patient age nor results of routinely performed blood test seems very useful in selecting children for lumbar puncture.

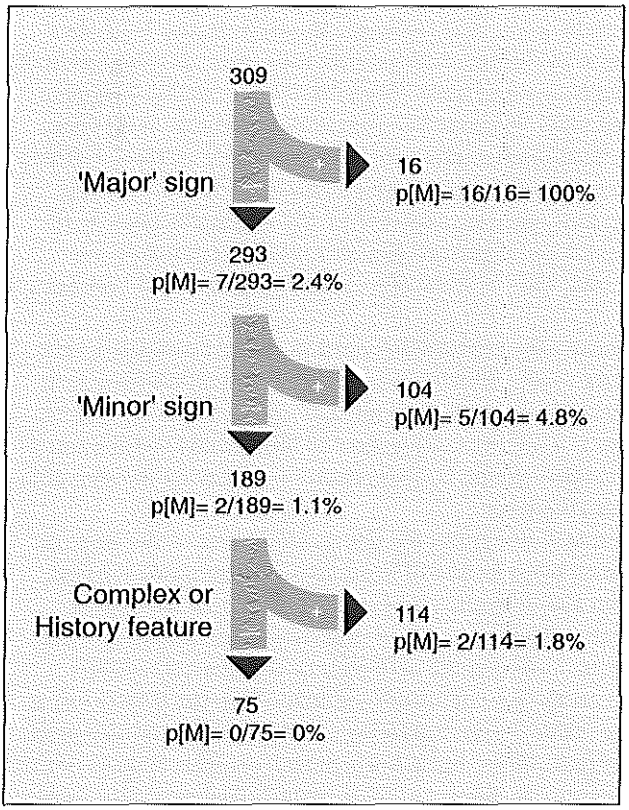
Several signs at the physical and neurological examination in the emergency room were found to be more helpful. Classic signs of this disease (here indicated as 'Major' signs) had high odds ratios for meningitis (Table 3.1.1). Seven children with meningitis lacked these signs, but presented with one or more other suspicious signs at the physical examination (so-called 'Minor' signs) or suspicious historical features. A seizure duration of 15 minutes or longer and a history of decreased responsiveness or drowsiness at home were especially indicative of meningitis.

To assess the diagnostic value of the presence or absence of any of the component indicators in these categories, several aspects of history, symptoms and signs were combined into the four categories of clinical information presented in Table 3.1.2. In this table the likelihood ratios and diagnostic values (i.e., the posterior probability of meningitis) are given when the indicators are either present or absent; 95% confidence intervals are added as an indication of the reliability of our findings, given the number of cases and referents that we could study.

All indicators had low likelihood ratios for absence and would make, when absent in an individual child, the presence of meningitis very unlikely. Except for a difference in the sensitivity of 'abnormal neurologic findings', the performance of all items is similar in both studies. Thus, we conclude that the 2 studies show essentially similar results.

Both studies indicate that children who present with seizures in the presence of meningitis are seriously ill and may well be in an advanced stage of the disease. This is illustrated by the reported increased mortality rate and high number of patients with permanent neurologic morbidity subsequent to meningitis when the disease is complicated by seizures. [1,3] Recently, on the other hand, three 'early' bacterial meningitis cases presenting with a seizure with fever were described. [21,22] These children, aged 5, 12 and 28 months, respectively, had no classic signs of the disease, and initial CSF analysis was normal. However, all had been drowsy and vomiting prior to the seizure or had had repeated seizures or a seizure during examination.

We assessed how many lumbar punctures would be done if a stepwise indication rule were applied using the clinical information in a sequence, i.e., first assigning children with obvious signs of serious disease to lumbar puncture, then those with the presence of Minor risk factors. To this end, we estimated the probability of meningitis among children showing a certain characteristic by dividing the observed number of meningitis cases with that characteristic by the sum of the number of meningitis cases with the characteristic plus the number of referents with the same characteristic multi-



3.1.2a

Figure 3.1.2a. Percentage of positive lumbar puncture findings using a stepwise indication rule. Children with positive clinical indicators will undergo lumbar puncture. Estimated prevalence of meningitis after each step p[M] is based on the prevalence of signs among 23 children with meningitis and among 69 out of 286 children without meningitis. Rule starts with items from the physical examination.

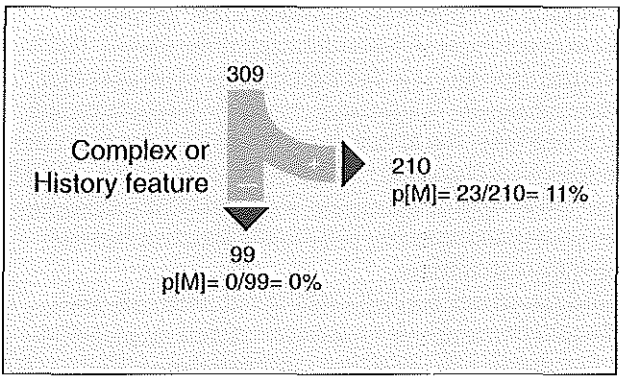


Figure 3.1.2b. As Figure 3.1.2a. Rule starts with items from the history.

plied by 286/69 (i.e., the inverse of the sampling fraction). This calculation assumes that the prevalence rates of the characteristics among the referents studied are equal to the prevalence rates of these characteristics among all children without meningitis. This assumption seems reasonable, since the 69 referents are a random sample from all the children without meningitis in the study. The results are shown in Figure 3.1.2. In a process of stepwise identification of children with positive indicators, the proportion of children with meningitis could be reduced from 7% to 0% (Figure 3.1.2a). If lumbar punctures had been performed in all children, 309 punctures would have been done, yielding 7% meningitis cases. Had lumbar punctures been doen only on those children with either a Major or a Minor sign of meningitis or a Complex or History feature, then 234 punctures would be done, yielding a total of 11.4% meningitis cases. If all children with positive indicators were considered eligible for lumbar puncture, no meningitis cases would be missed, and 75 of the 309 children (24%) would have been spared the puncture.

Different strategies of stepwise use of clinical information can be formulated; they all yield approximately the same result. Whichever category of clinical information is used first (i.e., the type of seizure, recent history or physical examination), all end by identifying all meningitis cases at a slightly varying 'cost' of false-positive results and—when used to select children for performing lumbar puncture—a varying number of (a posteriori) unnecessary lumbar punctures.

It is possible that in this retrospective study, the filling out of some of the items on the physical examination by the physician on call (e.g., signs of meningeal irritation, degree of coma) may have been biased by the physician's knowledge of the lumbar puncture results. To examine the diagnostic value of those items that would not have been biased by any test result, we looked at the performance of historical variables alone. Combinations of items on the type of seizure and items from the history had a high negative diagnostic value (Table 3.1.2), indicating a low probability of meningitis when a child presents without these items. In cases where both complex features of the seizure and suspicious symptoms in the history of the actual febrile illness were absent,

there were no meningitis cases (Figure 3.1.2b). If the decision to perform lumbar puncture were based only on the presence of symptoms from these two categories (and was independent of further information from physical and neurologic examination), no lumbar punctures would have been done in 32% (99/309) of all children.

There may be other factors that are of relevance to the likelihood of meningitis and the need for lumbar puncture. For instance, the time delay from seizure to evaluation in the emergency room may be important. Experienced clinicians take this lapse into account, since the typical child with a febrile seizure usually recovers within one hour after the attack, showing no clinical signs of severe illness thereafter (except, occasionally, for very high temperature). To arrive at any confident clinical decision rule, the findings of this study should be verified and extended, and this potentially important covariate (delay to evaluation) taken into account. Another indication for lumbar puncture might be the need to practice 'defensive' medicine for one reason or another or if parents insist on lumbar puncture. These situations will sometimes occur in practice but are to be distiguished from clinical indications for further investigation.

CONCLUSIONS

We conclude that meningitis in children who present with a seizure associated with fever can be ruled out on the basis of readily available clinical information. Our study does not support the need for routine lumbar puncture, provided that close follow up (or even a short clinical observation in the emergency room, to allow for a quick recovery) is available for children who are not undergoing lumbar puncture.

APPENDIX

The likelihood ratio (LR) is used to express the discriminatory power of diagnostic information and is defined as follows:

$$LR(finding) = \frac{probability\ of\ finding\ in\ diseased}{probability\ of\ finding\ in\ non\text{-}diseased}$$

or

$$LR(finding) = \frac{p(F|D)}{p(F|\overline{D})}$$

For each dichotomous clinical finding, e.g., a clinical indicator of meningitis, two LR's can be distinguished, one corresponding to the presence of the finding (LR+) and one to the absence of the finding (LR-):

$$LR+ = \frac{probability\ of\ finding'\ s\ presence\ in\ diseased}{probability\ of\ finding'\ s\ presence\ in\ non\text{-}diseased}$$

or

$$LR+ = \frac{p(F+|M)}{p(F+|\overline{M})}$$

and

$$LR- = \frac{probability\ of\ finding'\ s\ absence\ in\ diseased}{probability\ of\ finding'\ s\ absence\ in\ non\ -\ diseased}$$

or

$$LR- = \frac{p(F-|M)}{p(F-|\overline{M})}$$

In the present study a likelihood ratio LR+ = 1 implies that the finding is seen equally often in patients with and without meningitis; the finding adds no diagnostic information. A LR+ greater than 1 indicates an increased probability of meningitis if the finding is present, and a LR- between 0 and 1 indicates a lower probability of meningitis if the finding is absent. If the LR+ is infinite the finding is said to be pathognomic for meningitis, a LR- = 0 means that the finding excludes the disease. The likelihood ratio as defined above is used in the odds ratio form of Bayes' rule, which is used to calculate the (posterior) probability of the disease in light of clinical findings:

posterior odds = prior odds × likelihood ratio

or

$$\frac{p(D|\ finding)}{p(\overline{D}|\ finding)} = \frac{p(D)}{p(\overline{D})} \times LR(finding) \qquad \text{(Bayes' rule)}$$

This formula can be re-written to derive the (posterior) probability of D, given the finding:

$$p(D|\ finding) = \frac{1}{1 + \frac{p(\overline{D})}{p(D)} \times \frac{1}{LR(finding)}}$$

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3.2 Can meningitis be recognised by clinical assessment in children with seizures and fever? A two-year prospective study

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INTRODUCTION

It is crucial to distinguish benign intercurrent illness from central nervous system infection in previous healthy children who seize during a febrile illness. It is generally agreed that under the age of 6 months a seizure associated with fever should be considered as a sign of central nervous system infection until proven otherwise, and that therefore a lumbar puncture (LP) should be done. In contrast, for children between 6 months and 6 years, where seizures with fever are most prevalent, there is no consensus on the clinical indications for performing a LP. As a result, wide variation in diagnostic evaluation of febrile children with seizures exists. [1–3] In her recent monograph, Sheila Wallace states that 'lumbar puncture is undoubtedly the most controversial acute investigation'. [4]

The question is whether 'occult' meningitis can occur in these children, i.e., whether the seizure can be the sole manifestation of meningitis in a child who otherwise appears well. Several authors have recognized that young children with meningitis may lack classical meningeal signs. [5–7] Yet, there may be other signs and symptoms that indicate the presence of meningitis. [8–10]

Clinical identification of patients with meningitis after a seizure with fever has been attempted by a number of investigators. [11–13] In an earlier case control study we found that certain symptoms and signs from the physical examination in the emergency room discriminated between children with and without meningitis. [14] Clinical 'risk factors', as postulated in an older study, [12] were confirmed. Nevertheless, a Major drawback of this and all other previous studies is that they were retrospective and that the recording of items on the physical examination (e.g., signs of meningeal irritation, degree of coma) might have been biased by the attending physician's knowledge of the LP results. This bias may have exaggerated the relationship of these clinical findings with meningitis. Furthermore, recently other issues relevant to the probability of meningitis in individual children have been raised such as the duration and severity of the illness prior to the seizure and the time delay from seizure to clinical evaluation. [14,15]

As a continuation of our previous study, [14] a 2 years collaborative prospective study was undertaken. This focused on the clinical presentation of infants and children with a seizure associated with fever and addressed the issues raised in the literature. The pur-

pose was to determine the prevalence of meningitis and to evaluate the value of clinical data in diagnosing meningitis.

METHODS

Patients

Between February 1988 and February 1990, all children with a seizure associated with fever admitted to the emergency rooms of three urban hospitals in the western part of the Netherlands (Sophia Children's Hospital and the Zuiderziekenhuis in Rotterdam and the Juliana Children's Hospital in The Hague) were eligible for enrolment. These hospitals have 24 hours per day open paediatric emergency wards and receive about 15,000 referred and self-referred children in the emergency wards annually.

Previously healthy children between 6 months and 6 years of age with a temperature of at least 38.0° C, measured rectally at the emergency ward, were included. Children with a history of non-febrile seizures or with evident neurological abnormalities such as cerebral palsy and mental retardation were excluded.

At the emergency ward detailed data on the type of seizure, delay between seizure onset and presentation at the ward, used medication and the physical examination were obtained by house officers on a standard form. These data were recorded before results of the LP (if any) were available. Nuchal rigidity was scored as 'definite', 'doubtfull' or 'absent'. The pediatric Glasgow Coma Scale was used to record the level of consciousness. [16]

Decisions about blood tests and LP were left to the house officer. All children were either observed for 2 to 6 hours in the emergency ward or admitted to hospital, and all were re-evaluated within 72 hours after presentation by physical examination or by telephone. During this contact additional data on the recent illness, previous diseases and immunisations and family history of seizures were added. Selection of items to be recorded was based on the results of previous studies that have evaluated clinical items that discriminate between patients with and without meningitis. [11–14] They were divided into categories: General features, Complex features of the seizure (focal, multiple, prolonged), features from the History of the present illness, classic physical signs of meningitis (so called 'Major' signs) and other suspicious signs (so called 'Minor', but not less important signs).

After the resolution of the febrile illness the patient was seen in the outpatient clinic. During this contact the clinical outcome of the febrile episode was assessed.

Definition of meningitis

The final diagnosis (i.e., meningitis or no meningitis) was determined as follows: If a LP had been performed, a positive bacterial or viral culture from the cerebrospinal fluid was considered proof of meningitis. In case the culture remained sterile, but a clinical picture of meningitis developed during follow up associated with an initial cerebrospinal fluid-pleocytosis of at least 10 white blood cells/mm^3, meningitis was also considered to be present. Any pleocytosis above this level without a positive culture and

without further clinical signs of meningitis in children that quickly recovered was considered a false positive LP result. In case no LP had been performed, the final diagnosis was based on the clinical course during subsequent hospitalisation, on re-evaluation within 72 hours in the emergency room and at the final follow up contact.

Data analysis

The relations between the clinical characteristics and the presence of meningitis were assessed by calculating prevalence rate ratios, i.e., the probability of meningitis given the presence of a certain characteristic divided by the probability of meningitis in the absence of that characteristic. [17] The 95% confidence intervals were calculated according to Taylor. [17] If the entire confidence interval exceeds 1, the presence of the indicator marks an increased probability of meningitis at a 5% level of statistical significance. If the entire interval does not reach 1, the presence of the indicator is associated with a decreased probability of meningitis at a 5% level of statistical significance. Multivariate logistic regression analysis was used to examine the relation of the indicators with meningitis conditional on the presence of other indicators. The SAS® package was used for statistical computations. [18]

To assess the relevance of a clinical indicator likelihood ratios for the presence (LR+) and absence (LR-) of that indicator and their 95% confidence intervals were calculated (see Appendix A). The (posterior) probability of meningitis given the presence or absence of an indicator was assessed using Bayes' rule. [19] The observed prevalence rate of meningitis in this consecutive series was taken as the prior probability of meningitis.

RESULTS

During the 2 year period, 365 children with seizures and fever were included in the study. Among these, 21 cases (7%) of meningitis were diagnosed. Eleven cases were recognized already during referral and were admitted directly to the intensive care unit. The other 10 cases (3%) were first evaluated in the emergency room. There were no fatalities.

In 15 cerebrospinal fluid cultures revealed the cause of the infection: 13 were bacterial cases (*N. meningitidis*: 6, *H. influenzae*: 5, *S. pneumoniae*: 2) and 2 were viral cases (both enteroviruses). Four of the six remaining children with meningitis (more than 10 white blood cells/mm^3 in the cerebrospinal fluid and a clinical picture consistent with the disease on follow up) had been treated with anti-microbial agents prior to the seizure; in the two other cases the culture remained sterile without a proper explanation.

Of all children, 194 (53%) underwent LP. The proportion of children undergoing LP was equal in the 3 hospitals. In 10% the puncture was done within one hour after the seizure, in 70% between 1 and 6 hours after the seizure, and in 10% after 6 hours. In 54 instances a cerebrospinal fluid white blood cell count > 10/mm^3 was found. There were 26 recorded episodes of complications. These consisted of 5 (repeatedly) failed procedures, 19 traumatic taps (leading to small local haematoma and bloody

Table 3.2.1. Presence of selected clinical characteristics among cases and non-cases of meningitis.

Characteristic	*Meningitis cases (n = 21)*		*Non-cases (n = 344)*		*Rate Ratio (95% Confidence Interval)*
	No.	*(%)*	*No.*	*(%)*	
General features					
Male gender	11	(52)	200	(58)	0.8 (0.4–1.8)
Age < 12 months*	5	(25)	62	(18)	0.9 (0.3–2.4)
Age > 24 months*	5	(25)	105	(30)	0.8 (0.3–2.2)
Delay to evaluation > 1 hour†	11	(52)	129	(38)	1.8 (0.8–4.5)
Delay to evaluation > 6 hours†	4	(19)	24	(7)	2.8 (1.0–7.8)
Complex features of seizure					
Focal seizure	5	(24)	26	(8)	3.4 (1.3–11)
Duration > 15 min	4	(19)	44	(13)	1.5 (0.5–4.4)
Multiple seizures	11	(52)	88	(26)	2.9 (1.3–6.7)
At least one complex feature	15	(71)	137	(40)	3.5 (1.4–8.8)
History features					
At least 3 days ill	4	(19)	28	(8)	2.4 (0.9–6.8)
Seen by GP‡ in prev. 48 Hrs	9	(43)	118	(34)	1.4 (0.6–3.2)
Referred to hospital	12	(57)	130	(38)	2.1 (0.9–4.8)
Drowsiness at home	11	(52)	34	(10)	7.8 (3.5–17)
Vomiting at home	8	(38)	15	(4)	9.1 (4.2–20)
At least one history feature	15	(71)	150	(44)	3.0 (1.2–7.6)
Physical signs					
Temperature < 39°C**	7	(33)	71	(21)	1.8 (0.8–4.4)
Temperature > 40°C**	5	(24)	99	(29)	0.8 (0.3–2.1)
'Major' meningitis signs					
Petechiae	6	(29)	3	(1)	15.8 (8.0–31)
Nuchal rigidity, definite	8	(38)	6	(2)	15.4 (7.7–31)
Coma (GCS < 5)	3	(14)	14	(4)	3.4 (1.1–11)
At least one 'Major'sign	14	(67)	22	(6)	18.3 (7.9–42)
'Minor' meningitis signs					
Nuchal rigidity, dubious‡‡	8/13	(62)	53/338	(16)	7.6 (2.6–22)
Drowsiness (GCS 5–10)‡‡	12/18	(67)	23/330	(7)	17.0 (7.2–45)
Convulsing on examination	6	(29)	48	(14)	2.3 (0.9–5.7)
Paresis or paralysis on examination	3	(14)	7	(2)	5.9 (2.1–17)
At least one 'Minor' sign	5/7	(71)	68/322	(21)	8.8 (1.7–44)

* age 12–24 months as referent group;
† delay < 1 hour as referent group;
‡ GP: general practitioner or family physician;
** Temperature 39–40°C as referent group;
‡‡ Percentages and relative risk determined after exclusion of children with definite nuchal rigidity or coma.

Table 3.2.2. Presence of selected clinical characteristics among cases and non-cases of meningitis without 'Major' physical signs.

Characteristic	*Meningitis Cases (n = 7) No. (%)*	*Non-cases (n = 322) No. (%)*	*Rate Ratio (95% Confidence Interval)*
Age < 12 months*	3 (43)	58 (18)	1.9 (0.5–8.6)
Age > 24 months*	0 (0)	103 (32)	0 (0–3.2)
Complex features of seizure			
Focal seizure	3 (43)	24 (7)	8.3 (1.9–35)
Duration > 15 min	1 (6)	36 (11)	1.3 (0.2–10)
Multiple seizures	6 (86)	82 (25)	16.4 (2.0–134)
At least one complex feature	7 (100)	124 (39)	∞ (1.2–∞)
History features			
At least 3 days ill	1 (14)	25 (8)	1.9 (0.2–15)
Seen by GP in prev. 48 Hrs	2 (29)	108 (34)	0.8 (0.2–4.0)
Referred to hospital	4 (57)	116 (36)	2.3 (0.5–10)
Drowsiness at home	3 (43)	33 (10)	6.1 (1.4–26)
Vomiting at home	0 (0)	12 (4)	0 (0–30)
At least one history feature	3 (43)	138 (43)	1.0 (0.2–4.4)
Either a *complex* or *history* feature	7 (100)	202 (63)	∞ (0.9–∞)
'Minor' Physical signs			
Nuchal rigidity, dubious	4 (57)	49 (15)	6.9 (1.6–30)
Drowsiness (GCS 5–10)	4 (57)	21 (7)	16.2 (3.8–68)
Convulsing on examination	2 (29)	36 (11)	3.1 (0.6–15)
Paresis or paralysis on examination	2 (29)	7 (2)	14.2 (3.1–63)
At least one 'Minor' sign	5 (71)	68 (21)	8.8 (1.7–44)

* age 12–24 months as referent group.

cerebrospinal fluid) and two children that suffered prolonged back pain after the puncture (2 and 3 days). No permanent sequelae due to LPs were observed. A total of 269 children were admitted to hospital; 122 were treated with antibiotics of whom 35 were treated intravenously.

All 21 children with meningitis underwent LP at the first evaluation and were treated with intravenous antibiotics. None of the children with a cerebrospinal fluid white blood cell count lower than 10/mm^3 was treated for meningitis. In all 171 children (47%) who did not undergo LP, meningitis could be excluded on clinical ground at re-evaluation. Among the 344 children without meningitis no other known cause of the

Table 3.2.3. Discriminating ability of symptoms and signs suggesting meningitis. Likelihood ratios with 95% confidence interval (95% CI) and meningitis probabilities for the absence and presence of the characteristic.

Characteristic (See Table 1 for categories)	*Cases (n = 21)*		*Non cases (n = 344)*	
	No.	*(%)*	*No.*	*(%)*
At least one complex feature	15	(71)	137	(40)
At least one history feature	15	(71)	150	(44)
Either a complex or a history feature	20	(95)	221	(64)
At least one 'Major' sign	14	(67)	22	(6)
At least one 'Minor' sign, after exclusion of children with 'Major' signs[†]	5	(71)	68	(21)
At least one complex feature, after exclusion of children with 'Major' signs[†]	7	(100)	124	(39)

[*] p(MII+): posterior probability of meningitis when characteristic is present; p(MII-): posterior probability of meningitis when characteristic is absent; Calculated for meningitis prevalence in this series of 6% (21/365).
[†] Calculated for adjusted meningitis prevalence of 2.2% (7/322).

seizure apart from fever was found. They were considered to have suffered a febrile seizure.

Median age at presentation of all 365 patients was 19 months (range 6 to 52); 58% were boys. In 142 instances (39%) the child had been referred by a general practitioner, the remaining were self-referred.

Table 3.2.1 shows the presence of the selected clinical characteristics among children with and without meningitis. Meningitis occurred at all ages in equal proportion of boys and girls. A time lapse longer than 6 hours between the occurrence of the seizure and clinical evaluation was associated with an increased risk of meningitis (relative risk 2.8; 95% confidence interval 1.0-7.8). Focal seizures were associated with a higher risk of meningitis (relative risk 3.4; 1.3 to 11), as were multiple seizures (2.9; 1.3 to 6.7), and vomiting or drowsiness at home before the seizure (3.9; 1.4 to 10.9, and 7.1; 1.9 to 27.3, respectively). Children with meningitis had more often been ill for at least 3 days (2.4; 0.9 to 6.8) and were referred by a general practitioner (2.1; 0.9 to 4.8), but the latter two features' relative risks did not reach statistical significance. No positive or negative relation was observed between prior use of antibiotics or anticonvulsants and the presence of meningitis.

At the physical and neurological examination the classic 'Major' signs of meningitis (petechiae, definite nuchal rigidity) were seen mainly in children with meningitis. A

Characteristic present: *LR+ (95% CI)*		*p(MI+)** %	*Characteristic absent:* *LR- (95% CI)*		*p(MI-)** %
1.8	(1.3–2.4)	9.8	0.5	(0.2–0.9)	2.9
1.6	(1.2–2.2)	9.0	0.5	(0.3–1.0)	3.1
1.5	(1.3–1.7)	8.3	0.1	(0.02–0.9)	0.8
11.2	(6.3–17)	40.5	0.4	(0.2–0.7)	2.1
3.4	(2.0–5.7)	7.0	0.4	(0.1–1.2)	0.8
2.6	(2.3–3.0)	5.4	0	(0–0.9)	0

Glasgow Coma Scale score < 5 was observed in 17 children, and indicated an increased risk of meningitis (3.4; 1.1 to 11). Nevertheless, 7 children with meningitis (33%) lacked 'Major' signs.

After exclusion of children with definite nuchal rigidity, a doubtfull nuchal rigidity was observed in 8 of the remaining 13 meningitis cases and in 53 of the 338 non-cases (relative risk 7.6; 2.6 to 22). A Glasgow Coma Scale score between 5 and 10 indicated a 17 fold risk of meningitis. Paresis or paralysis on examination in the emergency room was also associated with an increased risk of meningitis (5.9; 2.1 to 17).

Table 3.2.2 shows the relation of clinical characteristics with meningitis in children without 'Major' physical signs. Of the 7 remaining children with meningitis, 3 were < 12 months of age and all were < 24 months. Thus, older children present more often with classical signs. All seizures of these 7 meningitis cases had Complex features. Drowsiness at home before the occurrence of the seizure was indicative of meningitis, as were all individual 'Minor' physical signs.

In multivariate logistic regression analyses focal and multiple seizures, vomiting and lowered consciousness at home appeared to be the strongest indicators of meningitis, apart from the classical signs.

The ability of characteristics to distinguish between meningitis- and non-meningitis-cases is shown in Table 3.2.3. Petechiae, nuchal rigidity or coma were seen in 14 out

of 21 meningitis cases (67%); in non-cases these 'Major' signs were seen in 6%. Thus, the likelihood ratio when any of these signs is present (LR+) was 11.2 (95% confidence interval 6.3 to 17) and the posterior probability of meningitis 26%. Other characteristics (Complex or History features, 'Minor' signs) had a lower LR+ and result therefore in lower posterior probabilities. On the other hand, all these indicators had low likelihood ratios when absent (LR-), leading to a very low posterior probability of meningitis when these indicators were absent.

We assessed the yield of LP if an inclusive indication rule based on clinical information would be used. The results are shown in Table 3.2.4. Using various stepwise decision rules, meningitis could be excluded, saving between 120 (33%) and 198 (54%) of children the LP (Table 3.2.4, No. LP column). To put these findings in further perspective, we evaluated two main strategies in the management of children with seizures and fever. For this purpose, we compared two simple diagnostic scenarios using the techniques of decision analysis. In this analysis we assumed that eventually all cases of meningitis are treated, but we incorporate the possibility that *delayed* treatment is less effective than immediate treatment. Details are given in the Appendix B, Tables 3.2.5 and 3.2.6.

The analysis showed that more than 40% of LPs can safely be omitted when clinical information is used. If meningitis is present and detected after a delay, thus doubling case mortality and morbidity, *and* if the LP test is a perfect test (i.e., sensitivity and specificity both 1.0), an increased mortality and permanent sequelae rate of 4 and 7 per 10,000 children with seizures and fever can be expected, respectively (Table 3.2.6, G). If LP is assumed to be associated with fatal and non-fatal complications, the strategy of routine LP leads to overall excess mortality and morbidity.

DISCUSSION

The main finding of our study is that meningitis does not occur in children with seizures and fever in the absence of other clinical signs and symptoms. As in our previous study, [14] 2 out of 3 children with meningitis had classical signs of the disease. In those without these 'Major' signs, complex seizures and a suspicious history had high *negative* diagnostic values, i.e a low meningitis probability when a child presents *without* these items. In the absence of any Complex feature and any suspicious symptom, there were no meningitis cases in the present study. These clinical risk factors have been identified in earlier studies, [12,14] and are now confirmed in our prospective series. Further, in our study the child's age, gender, and degree of fever had no diagnostic value. Yet, as this study was done in the emergency room setting, it is noted that its results may not be applicable to the situation in which the family physician or general practitioner evaluates the child.

In our previous study we suggested a possible discriminating role for time-delay from seizure to evaluation. [14] Our present finding that this delay indicates an increased meningitis risk appeared to be partially due to referral. General practitioners manage up to 50% of all seizures with fever in the Netherlands, [20,21] and after such an attack other-

Table 3.2.4. Clinical strategies for lumbar puncture (LP) in 365 children with a seizure associated with fever. Total number of LPs performed (No. LP); observed prevalence of meningitis (No. Men); missed meningitis cases in children having not undergone LP (No. Men missed).

	Indication for LP	*No. LP*	*No. Men (%)*	*No. Men missed*
	Routine*	365	21 (6)	0
I	Presence of a *Major sign*: definite nuchal rigidity or coma (GCS < 5) or petechiae	36	14 (39)	7
II	As I, also if a *Minor sign* is present: dubious nuchal rigidity, drowsiness, convulsing, and or paresis or paralysis on examination	109	19 (17)	2
III	As II, also if a *Complex feature* is present: focal seizure, duration > 15 min, and or multiple seizures	205	21 (10)	0
IV	As I, also if a *Complex feature* is present:	167	21 (12)	0
V	As I, also if a *History feature* is present: at least three days ill, drowsiness, and or vomiting at home	177	17 (10)	4
VI	As I, also if either a *Complex feature* or a *History feature* is present	245	21 (9)	0

* i.e., in all children who present with a seizure associated with fever.

wise well children are simply not referred. Yet, in situations without a general practitioner, delayed self-referral to an emergency room may also indicate serious illness.

In the setting of the present study the overall prevalence of meningitis was 7%. Eleven of the 21 cases were already clinically recognized before hospital admittance; these children were so sick that treatment in the intensive care unit was indicated. Thus, 10 meningitis cases (or 3%) were present among those 354 children that were

evaluated in the emergency room. It may be argued that the true meningitis prevalence may have been higher, because not all children had cultures of cerebrospinal fluid. However, in the course of 72 hours follow-up none developed symptoms which prompted further examinations, which suggests that no (clinically relevant) meningitis cases were missed.

The findings of our prospective study correlate with those of studies with a different design. Recently, Green et al. retrospectively reviewed 503 consecutive children with meningitis. [22] None had bacterial meningitis manifesting solely as a simple seizure with fever. The authors concluded that 'occult meningitis is either extremely rare or nonexistent' and that commonly taught indications for performing LP in children with fever and a seizure appear to be unnecessarily broad.

The decision to perform LP is influenced by many factors. One is surely the perceived probability of meningitis in children with seizures and fever. Other factors are the hazards and drawbacks of routine LPs, potential dangers of a delayed diagnosis of men ingitis, sensitivity and specificity of the LP test itself, and the reliability of the history and physical findings. In this latter respect, one should be extra cautious if antiepileptic drugs (e.g., diazepam) or antibiotics have been used prior to evaluation, for they are suspected to alter the clinical presentation of meningitis. [10] Finally, the fact that in teaching hospitals the emergency room is most often staffed by junior doctors may add arguments both for and against routine LP.

From our decision analysis it followed that only if delayed treatment leads to a substantial increase in meningitis mortality and morbidity as compared to early treatment, a routine LP approach yields an on average more favourable result. Yet, this is achieved at the cost of several hundreds LPs in children without meningitis per 1,000 children with a seizure with fever. On the other hand, if LP is actually associated with fatal and non-fatal complications, however low in frequency, performing routine LPs will lead to excess mortality and morbidity. Thus, clinical policy should be guided by weighing medical costs and benefits.

CONCLUSIONS

Several studies, including the present one have shown that the probability of meningitis in infants and children with seizures and fever is low and depends on the clinical presentation. Meningitis may occur in the absence of signs of meningeal irritation. Therefore, other signs such as a longer existing febrile illness, vomiting, drowsiness prior to clinical evaluation, and focal or repeated seizures must be recognized. If such symptoms are also absent, meningitis is highly improbable. We conclude that if clinical information is used appropriately there is no need for routine investigation of cerebrospinal fluid in children who present with a seizure associated with fever. Such routine testing may even be dangerous.

APPENDIX A

The likelihood ratio (LR) is used to express the discriminatory power of diagnostic information and is defined as follows:

$$LR(finding) = \frac{probability\ of finding\ in\ diseased}{probability\ of finding\ in\ non\ -\ diseased}$$

or

$$LR(finding) = \frac{p(F|D)}{p(F|\overline{D})}$$

For each dichotomous clinical finding, e.g. a clinical indicator of meningitis, two LR's can be distinguished, one corresponding to the presence of the finding (LR+) and one to the absence of the finding (LR-):

$$LR+ = \frac{probability\ of finding'\ s\ presence\ in\ diseased}{probability\ of finding'\ s\ presence\ in\ non\ -\ diseased}$$

or

$$LR+ = \frac{p(F+|M)}{p(F+|\overline{M})}$$

and

$$LR- = \frac{probability\ of finding'\ s\ absence\ in\ diseased}{probability\ of finding'\ s\ absence\ in\ non\ -\ diseased}$$

or

$$LR- = \frac{p(F-|M)}{p(F-|\overline{M})}$$

In the present study a likelihood ratio LR+ = 1 implies that the finding is seen equally often in patients with and without meningitis; the finding adds no diagnostic information. A LR+ greater than 1 indicates an increased probability of meningitis if the finding is present, and a LR- between 0 and 1 indicates a lower probability of meningitis if the finding is absent. If the LR+ is infinite the finding is said to be pathognomic for meningitis, a LR- = 0 means that the finding excludes the disease. The likelihood ratio as defined above is used in the odds ratio form of Bayes' rule, which is used to calculate the (posterior) probability of the disease in light of clinical findings: [19]

posterior odds = prior odds × likelihood ratio

or

$$\frac{p(D|finding)}{p(\overline{D}|finding)} = \frac{p(D)}{p(\overline{D})} \times LR(finding) \qquad \text{(Bayes' rule)}$$

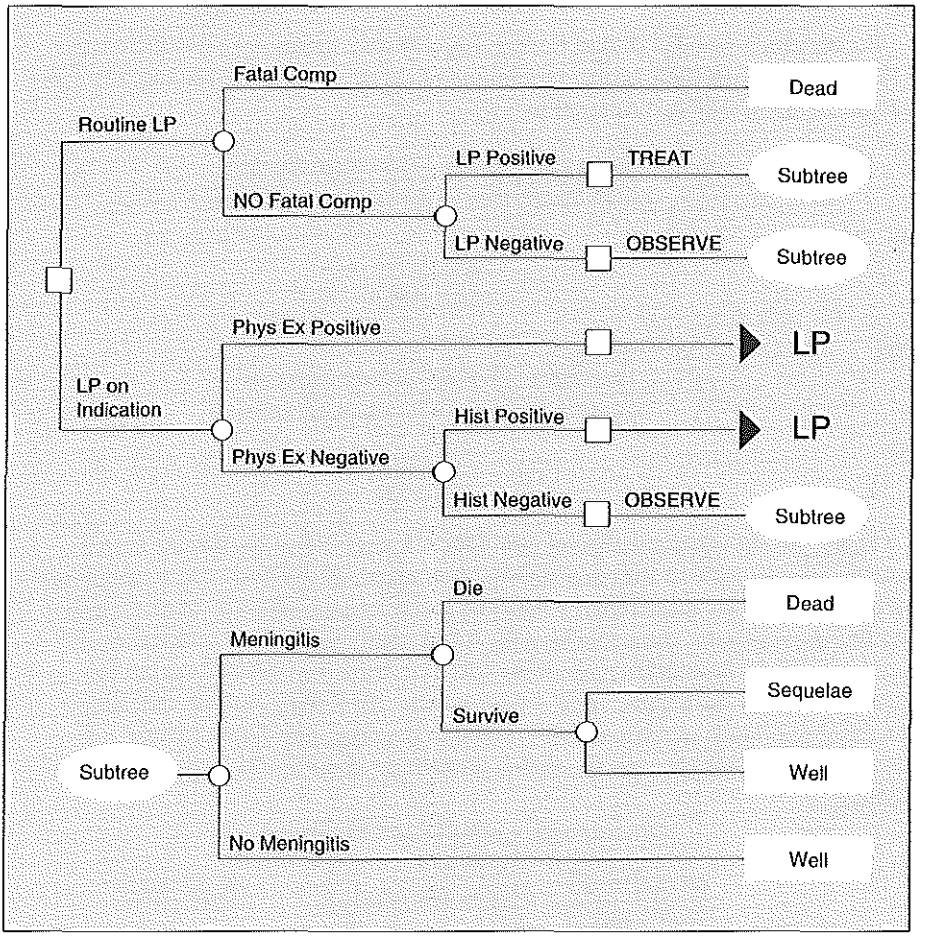
This formula can be re-written to derive the (posterior) probability of D, given F:

$$p(D|finding) = \frac{1}{1 + \frac{p(\overline{D})}{p(D)} \times \frac{1}{LR(finding)}}$$

APPENDIX B

Decision model

The contrast in the decision analysis is between routine LP for all children, and LP performance on indication, i.e. when the history and physical examination are suspicious to some extent. The analysis balances the number of children that undergo LP in each of the two strategies against the risk of delayed antimicrobial treatment in case of meningitis. We considered all events following either of the two strategies to occur in



3.2.1

Figure 3.2.1. Decision tree used in analysis of diagnostic strategies. The subtree shown in the lower part is followed for each branch of the primary tree above ending in 'Subtree'. Any lumbar puncture (LP) is first followed by either a fatal complication due to LP (Fatal Comp), or NO Fatal Comp. Then the LP-result follows. Phys Ex: physical examination; Hist: history; TREAT: start empirical antibiotics; OBSERVE: expectant observation either at home or in hospital ward.

the first 12 hours after presentation to the emergency room. We assumed that in each strategy meningitis, when present, is finally detected and treated accordingly.

The Figure shows the decision tree used to evaluate the alternative management strategies. The branches of the tree consist of decision options (squares), subsequent chance events (circles) and outcomes (boxes). The LP test result (i.e., pleocytosis) can be either positive or negative. Similarly, the 'physical examination'-test (nuchal rigidity or coma) can be positive or negative. In case of a positive 'physical examination'-test a LP is performed. In case the test is negative, a second 'test', the history, is taken. LP follows if this test is positive, if it is negative close observation for up to 12 hours follows.

Probabilities

Published surveys indicate that the prevalence of meningitis among children with seizures and fever in paediatric emergency wards is about 1%. [23] Other investigators have found 3% to 7% meningitis cases, but these hospital based series include seizures in children with an already recognized meningitis. [11-14] Mortality from bacterial meningitis lies between 5% to 10%. [24-27] In those patients whose meningitis is complicated by seizures, the mortality is higher, ranging from 10% to 50%. [6,26] Permanent neurological sequelae occur in 15% to 50% of survivors; [24-27] the risk of sequelae seems higher in patients with seizures. [6,25,26]

Several investigators have pointed to the low sensitivity of LP in the early stages of meningitis and the risk of relying on an initially reassuring test. [28-31] Conversely, there are reports of pleocytosis after seizures or head trauma, in the absence of infection. [32] There are other situations when the LP result is unreliable. [33-35] Thus, both false negative and false positive LP results may mislead the clinician. False negatives are likely the most dangerous.

The influence of complications due to the LP procedure itself, both fatal and non-fatal, was considered. We assumed that eventually all cases of meningitis were treated, but we incorporated the possibility that *delayed* treatment is less effective than immediate treatment. The simplifying assumption was made that non-fatal sequelae due to complications of LP are clinically as serious as non-fatal sequelae of meningitis. It was also assumed that anaphylactic reactions to antimicrobial drugs are treatable in this setting and are not associated with fatal and non-fatal complications. Except for a few case reports, [36-38] no studies on the fatal and non-fatal complication rate of LP could be found in the medical literature. Also, there are very few reports on the outcomes of children who were not immediately treated after a clinical diagnosis of meningitis was made. [39] We therefore estimated plausible values for these variables, and initially evaluated the model ignoring these complications.

Evaluation

The decision model was used to calculate for each strategy the probability of either death or survival with or without permanent sequelae. Thus, neither utilities attached to these outcomes nor economic costs are formally considered in the analysis. Because some degree of uncertainty surrounds all probabilistic events, a sensitivity analysis was

Table 3.2.5. Probability estimates used to compare diagnostic strategies.

Variable	*Point estimate*	*Plausible range*	*Reference*
Presence of meningitis	0.03	0.01–0.10	[11–14,23]
Death due to meningitis	0.08	0.03–0.15	[6,24,26]
Permanent sequelae due to meningitis	0.20	0.10–0.35	[6,24–27]
Test Characteristics			
Sensitivity LP	0.95	0.90–1.0	[28–32]
Sensitivity PE	0.70	0.50–0.85	[11–14, PR]
Sensitivity HI	0.80	0.70–0.90	[11–14, PR]
Specificity LP	0.95	0.80–1.0	[28–34]
Specificity PE	0.90	0.85–0.95	[11–14, PR]
Specificity HI	0.50	0.35–0.65	[11–14, PR]
Complication rate of LP			
Fatal	0	0–0.005	*
Non-fatal	0	0–0.005	*
Relative efficacy of early vs. late antimicrobial treatment of meningitis	1	0.5–1	*

LP, lumbar puncture-test (presence of pleocytosis); PE, physical examination-test; HI, recent disease history-test; PR, present study.
* No case series were found in the literature.

performed, i.e. the values of one or more variables were varied and calculations were repeated to determine the influence of the uncertainty in these variables' probabilities on the outcome. Probabilities for the calculations and plausible intervals were taken from the literature as discussed above; they are summarised in Table 3.2.5.

We calculated the number of lumbar punctures, meningitis cases, fatalities, children with permanent sequelae and children that were either unjustly treated for meningitis or, on the other hand treated with a delay for a hypothetical cohort of 10,000 children with a seizure associated with fever, by strategy. The results of the analysis are summarized in Table 3.2.6. Eight sets of assumptions were tested. The number of children in the outcomes Dead, Sequelae and Well was mainly determined by the overall probability of meningitis and its associated mortality and morbidity. If the LP procedure itself, antimicrobial treatment and treatment delay had no (added) mortality and morbidity,

Table 3.2.6. Results of decision analysis. Occurrence of various outcomes in cohort of 10,000 children with a seizure associated with fever, by strategy.

Strategy	*LPs*	*MEN*	*treated immediately*	*treated after delay*	*DEAD*	*SEQ*	*WELL*
A: Given the point estimates from Table 3.2.5							
LP on indication	5,617	300	535	32	24	55	9,921
Routine LP	10,000	300	770	15	24	55	9,921
Difference	*-4,383*	–	*-235*	*17*	*0*	*0*	*0*
B: If LP is a perfect test (i.e. sensitivity and specificity both 1.0)							
LP on indication	5,617	300	282	18	24	55	9,921
Routine LP	10,000	300	300	0	24	55	9,921
Difference	*-4,383*	–	*-18*	*18*	*0*	*0*	*0*
C: If LP is associated with 0.005 fatality and 0.005 nonfatal permanent sequelae							
LP on indication	5,617	300	535	32	52	83	9,865
Routine LP	10,000	300	770	15	74	104	9,822
Difference	*-4,383*	–	*235*	*-17*	*-22*	*-21*	*43*
D: If delayed treatment (after observation) leads todouble meningitis fatality and sequelae							
LP on indication	5,617	300	535	32	27	60	9,913
Routine LP	10,000	300	770	15	25	58	9,917
Difference	*-4,383*[*]	–	*-235*	*17*	*2*	*2*	*-4*
E: If the prior probability of meningitis is 0.10							
LP on indication	5,890	1,000	1140	107	80	184	9,736
Routine LP	10,000	1,000	1400	50	80	184	9,736
Difference	*-4,110*	–	*-260*	*57*	*0*	*0*	*0*
F: If PE and HI sensitivity and specificity take Table 3.2.5's lowest values and LP is a perfect test							
LP on indication	7,070	300	255	45	24	55	9,921
Routine LP	10,000	300	300	0	24	55	9,921
Difference	*-2,930*	–	*-45*	*45*	*0*	*0*	*0*
G: As F and delayed treatment leads to double meningitis fatality and sequelae							
LP on indication	7,070	300	255	45	28	62	9,910
Routine LP	10,000	300	300	0	24	55	9,921
Difference	*-2,930*[**]	–	*-45*	*45*	*4*	*7*	*-11*

LPs, number of lumbar punctures; MEN, number of meningitis cases; DEAD, fatalities; SEQ, permanent sequelae; WELL, total resolution; PE, physical examination-test; HI, recent disease history-test.

[*] On average 3204 extra LPs would be necessary to save one additional life.

[**] On average 814 extra LPs would be necessary to save one additional life.

no differences between the two diagnostic strategies in the above outcomes were found. Yet, in the strategy starting with a physical examination a fair reduction in number of LPs and post-hoc unnecessary treatments was achieved, at the cost of a small number of meningitis cases that would be treated after some delay.

The number of LPs saved was a function of the probability of meningitis, and the specificity (i.e. true negatives) of both the physical exam and disease history. The specificity of history (at present 0.50) had the greatest influence; therefore, identification of historical features with a high specificity for meningitis should be pursued.

If the LP procedure, if the treatment, or if a treatment delay bore additional mortality or morbidity risks, then the small differences in outcomes between the two strategies would be determined by the medical costs attendant to this risk. Risks from LPs or from treatment biased the conclusions in favour of the 'physical examination' strategy, whereas any increase in mortality and morbidity due to a delayed meningitis treatment biased the conclusions in favour of the routine LP strategy.

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4
Management of recurrent seizures

4.1 Seizure recurrence after a first febrile seizure—a multivariate approach

Martin Offringa, Gerarda Derksen–Lubsen, Patrick M Bossuyt, and Jacobus Lubsen

INTRODUCTION

The probability of seizure recurrence after an initial febrile seizure in children remains uncertain. [1–5] Population-based studies have indicated that three or more recurrent seizures occur in only 4.1% to 9%. [1,3] On the other hand, studies from referral settings have found the risk of ≥ 3 recurrences to be as high as 35%. [6] This uncertainty is due both to limited follow-up and to the absence of information about the combined predictive value of multiple so called 'risk factors'.

Most studies have limited their follow-up to the first recurrence, and have evaluated the predictive value of single risk factors through univariate analyses. In previous studies, complex initial seizures, [1,2] the presence of a first degree family history of seizures of any kind, [1,2] body temperature at first febrile seizure, [6–8] and age have been found to be associated with an increased risk of recurrences. [1,3,9] Yet, a recent meta-analysis has indicated that none of these risk factors alone could identify children at high and low risk of recurrent seizures. [10] This conclusion is consistent with the suggestion of others, [2,3,11] that the risk of recurrent febrile seizures could be predicted better by a combination of risk indicators.

Simple recurrent febrile seizures usually do not lead to permanent damage. However, multiple recurrent seizures during subsequent febrile episodes are disturbing and—although to date little information on the subject is available—potentially may result in prolonged seizures with a risk of subsequent neurologic impairment. Therefore, prediction of recurrences—and particulary multiple recurrences—could identify children who may benefit from preventive treatment, and could spare others from the inconvenience and risk of retarded cognitive development associated with long-term administration of antiepileptic drugs. [12] In this respect the critical time period during which the child is at risk of further seizures after the initial febrile seizure is of particular relevance. More insight into this matter may lead to adjustment of the prophylactic treatment duration for individual children.

We describe the course and outcome after a first febrile seizure of a cohort of Dutch children, with special emphasis on the changes in the risk of recurrence over time. The combined predictive value of multiple clinical variables at the first febrile seizure for

future seizure recurrence is assessed, as well as the role of the child's age in the hazard of recurrent seizures.

PATIENTS AND METHODS

The study was carried out at the emergency room of the Sophia Children's Hospital in Rotterdam. This is a teaching hospital, which keeps full patient records and has a 24-hour emergency service. febrile seizure was defined according to the National Institutes of Health (NIH) consensus statement. [13] All previously healthy children aged between 6 months and 5 years, presenting with a first febrile seizure and a body temperature of 38.5° C (101.3° F) or higher, but without evidence of intracranial infection or defined cause (e.g., metabolic dysregulation) between March 1985 and March 1987 were included. Children with a history of non-febrile seizures or with neurological abnormalities such as cerebral palsy and mental retardation were excluded, since their subsequent course is determined mainly by their basic disorder. Furthermore, those who were treated with continuous phenobarbitone or valproate were excluded because we wanted to study the natural history in previous healthy, untreated children. Seizures were defined as complex if they had lasted for more than 15 minutes, had focal features or reccurred within 24 hours.

History and clinical data on admission were retrieved from the patient's record. The outcome variable was the recurrence of seizures during the follow-up period ending on 1 September 1989.

In August 1989, all children were contacted by telephone after a mailed announcement. Addresses and telephone numbers of families who had changed their address were retrieved from municipal registries. If contact could not be established the family physician provided follow-up information. All follow-up interviews were carried out by one investigator (MO). The number and type of recurrent seizures, if any, as well as the time intervals between subsequent seizures, were recorded. Seizures were considered non-febrile if they had occurred at a body temperature of 37.5° C or below.

A cumulative proportion of children with recurrences after each seizure was estimated using the product limit method of Kaplan-Meier; [14] strata were compared using the log-rank test. Differences in age between children with and without recurrences were assessed with the student t-test after log-transformation of the values; [15] p-value ≤ 0.01 was considered significant.

The hazard was assessed of seizure recurrence and of 3 or more recurrent seizures during follow-up. To evaluate potential risk factors, we used univariate and multivariate Cox proportional hazards regression models. [16] All risk factors were dichotomized; children lacking the attribute represented the reference category. Age at onset was diveded into 3 groups, with age between 12 and 30 months as the reference category. To compare rates in children with and without a certain factor, hazard rate ratios with 95% confidence intervals were calculated from the factors' regression coefficients and their standard errors. In the univariate analyses they are referred to as 'crude' rate ratios. A factor with a rate ratio significantly higher than 1 would be associated with an increased

risk of recurrent seizures, while a factor with a rate ratio significantly lower than 1 would be associated with a decreased risk.

Multivariate proportional hazard models were used to examine the combined influence of the risk factors on the probability of subsequent febrile seizures. Covariates were eliminated from the model using the partial likelihood ratio test, with 0.10 as the p limit for exclusion. [17] Rate ratios, 'adjusted' for the presence of other factors retained in the multivariate model, and their 95% confidence intervals were calculated using the regression coefficients and their standard errors.

The combined effect of all relevant risk factors on the probability of at least one recurrence was assessed. A composite risk score for each child in the study was calculated using the factors' weights (i.e., the regression coefficients from the final parsimonious multivariate model) and an indicator coding 0 if the attribute was absent and 1 if the attribute was present. Patients were arranged in order of increasing score value and then divided into 3 risk groups: a score of 0 (zero) implied a 'medium' risk (no factors present), a score below 0 a 'low' risk (mainly 'protecting' factors), and above 0 a 'high' risk. Stratified Kaplan-Meier analysis for these 3 levels of composite risk was performed. Similar scores were calculated using the regression coefficients from the multivariate model for 3 or more recurrent seizures. Two groups were formed: children scoring below 0 ('low' risk) and ≥ 0 ('high' risk). This score for the risk of multiple recurrences was used to asses the risk of any seizure recurrence for the entire cohort. Univariate statistics and Kaplan-Meier product limit estimators were calculated, using the SAS-PC statistical package (SAS Institute Inc., Cary, NC); for the proportional hazard models the BMDP package was used (BMDP Statistical Software, Inc., Los Angeles, CA).

RESULTS

Altogether 175 children met the inclusion criteria, of whom six had a known neurological abnormality; these were excluded. Eight children who had received long-term antiepileptic treatment after the initial febrile seizure were also excluded from the risk analyses. Six of them apparently were treated for complex features of the first seizure in combination with an age at onset less than one year; the other two children had recurring febrile seizures within 24 hours, with partial features in one. Despite monitored treatment, 3 of these 8 children had recurrent seizures, one of whom had frequent nonfebrile seizures. Six were lost to follow-up shortly after the initial febrile seizure.

Median age at onset of the remaining 155 children was 18 (range 6 to 54) months. In most instances their febrile seizures were associated with upper respiratory-tract infections, diarrhoea or fever of short duration. They all recovered without complications within several days. Follow-up information was obtained from the parents in 139 instances, and from the family doctor in 16. In all instances, parents and family physicians could recall the dates of the recurrent seizures. Median follow-up time was 38 (range 27 to 60) months.

Table 4.1.1a. Number (No.) of recurrences, crude and adjusted hazard rate ratios for at least one recurrence in 155 children, initially not treated with anti-convulsant prophylaxis.

Factor	*At Risk*	*No.*	*Hazard Rate Ratio* with 95% CI*			
			Univariate analysis		*Multivariate analysis*	
Gender						
female	65	24	rc			
male	90	34	1.03	*(0.61–1.73)*	†	
Age at onset						
< 12 months	25	11	1.25	*(0.64–2.46)*	†	
12–30 months	99	38	rc		rc	
≥ 30 months	31	9	0.68	*(0.32–1.40)*	0.43	*(0.19–0.94)*
Family seizure history‡						
none	128	39	rc		rc	
unprovoked	7	5	3.76	*(1.50–9.41)*	3.62	*(1.40–9.21)*
febrile	20	14	3.41	*(1.87–6.24)*	3.92	*(2.08–7.27)*
Initial seizure						
duration ≤ 15 min.	136	53	rc			
duration > 15 min.	19	5	0.74	*(0.30–1.86)*	†	
generalized	147	55	rc			
focal	8	3	0.85	*(0.27–2.72)*	†	
single	130	44	rc		rc	2.45
multiple	25	14	2.07	*(1.13–3.76)*	2.45	*(1.27–4.64)*
Temperature						
< 40.0° C	96	41	rc		rc	
≥ 40.0° C	59	17	0.63	*(0.35–1.12)*	0.46	*(0.25–0.82)*

* Hazard Rate Ratio compared with reference category (rc);
† not retained in stepwise multivariate proportional hazard model;
‡ only first-degree family.

Recurrent seizures

Of the 155 initially untreated children 58 (37%) had at least one, 47 (30%) at least two and 27 (17%) at least three recurrent seizures. Five (3%) had unprovoked non-febrile seizures, in one case as the first recurrence; in the other four the unprovoked seizures occurred after two recurrent febrile seizures; four children had more than five recurrences. Only one child experienced a complex recurrent seizure. None had any neurological sequelae.

Table 4.1.1b. Number (No.) of ≥3 recurrences, crude and adjusted hazard rate ratios for ≥3 recurrences in 155 children, initially not treated with anticonvulsant prophylaxis.

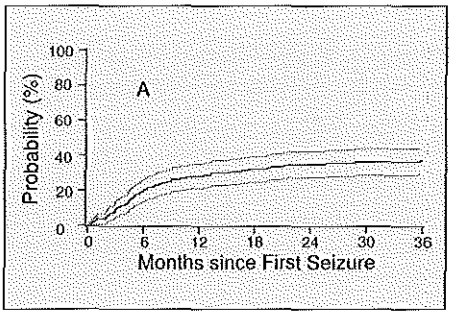
Factor	*At Risk*	*No.*	*Hazard Rate Ratio* with 95% CI* *Univariate analysis*		*Multivariate analysis*	
Gender						
female	65	14	rc			
male	90	13	0.63	*(0.29–1.34)*	†	
Age at onset						
< 12 months	25	7	1.56	*(0.65–3.74)*	†	
12–30 months	99	18	rc		rc	
≥ 30 months	31	2	0.34	*(0.08–1.47)*	0.30	*(0.07–1.25)*
Family seizure history‡					rc	
none	128	18	rc		rc	
unprovoked	7	3	3.46	*(1.04–11.50)*	5.04	*(1.42–17.50)*
febrile	20	6	1.90	*(0.77–4.72)*	2.98	*(1.23–7.18)*
Initial seizure						
duration ≤ 15 min.	136	24	rc			
duration > 15 min.	19	3	1.13	*(0.34–3.76)*	†	
generalized	147	25	rc			
focal	8	2	1.49	*(0.35–6.30)*	†	
single	130	22	rc			
multiple	25	5	1.22	*(0.46–3.23)*	†	
Temperature						
< 40.0° C	96	21	rc		rc	
≥ 40.0° C	59	6	0.57	*(0.22–1.48)*	0.47	*(0.19–1.11)*

* Hazard Rate Ratio compared with reference category (rc);
† not retained in stepwise multivariate proportional hazard model;
‡ only first-degree family.

Risk factors

Univariate analysis revealed that a family history of febrile or unprovoked recurrent seizures and a multiple initial febrile seizure were associated with an increased risk of recurrent seizures, while a body temperature of 40.0° C. or higher at the initial seizure and an age of ≥ 30 months were associated with a reduced risk. These factors were all retained in the multivariate model (Table 4.1.1a).

Children with ≥ 3 recurrences had a lower median age at the initial seizure compared to children with none and one or two recurrent febrile seizures (13, 19 and 20



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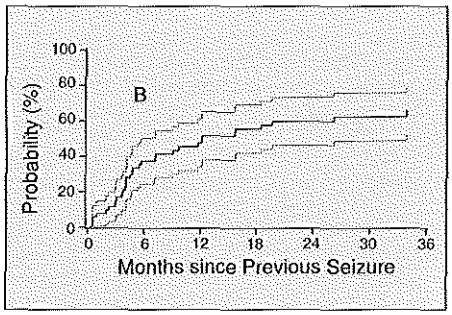


4.1.1b

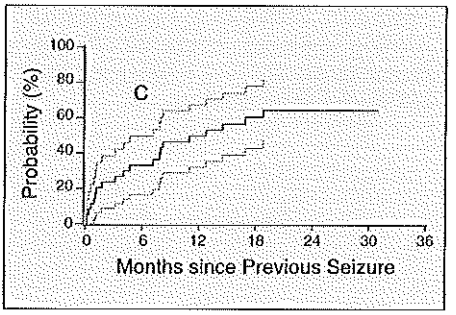
months, respectively). For this outcome a family history of febrile or unprovoked seizures was selected as a risk factor in the multivariate model; a temperature ≥ 40.0° C and age ≥ 30 months at the initial febrile seizure were also selected and associated with decreased risk, but reached no statistical significance (Table 4.4.1b). Age at the first or second recurrence differed between children with and without multiple recurrences: median 20 vs. 28 months for age at the first recurrence and median 26 vs. 32 months for age at the second recurrence; only the difference between the ages at the first recurrence was significant ($p = 0.01$).

The time interval between the initial seizure and the first and second recurrences did not differ between children with and without multiple recurrences (median 5.1 vs. 5.2 months and 4.8 vs. 7.0 months, respectively). All 5 children with recurrent non-febrile seizures had a complex initial febrile seizure, four of whom had a temperature below 40.0° C. Two were younger than 12 months at the initial febrile seizure, and none older was than 30 months.

Recurrence hazard

Kaplan-Meier curves for the first, second and third recurrence (155, 58 and 47 children at risk, respectively) with 95% confidence intervals indicated that the hazard of recurrence was highest during the first months after a seizure and declined rapidly after several months without seizures (Figure 4.1.1). The recurrence rate in children without seizures during the first six months declined from 21% to 11%; during the first 12 months of follow-up the recurrence rate declined to 4%. After a first recurrent seizure the rate of further recurrences was 37% in the first 6 months and—after 6 months without seizures—22% in the second half year. After the second seizure recurrence the rate of further recurrences was 34% in the first, and 25% in the second half year.

Kaplan-Meier analysis using family history of seizures and body temperature at the initial febrile seizure, revealed different two-year recurrence rates for children who had none (35%), either (80% with positive family history, temperature < 40.0° C; 18% with negative family history, temperature ≥ 40.0° C) or both of these factors (55%). First febrile seizures at a body temperature above 40.0° C in children with a family his-



4.1.1c

Figure 4.1.1 Probability of seizure recurrence in initially untreated children. A) after initial febrile seizure (155 at risk), B) after first recurrence (58 at risk), C) after second recurrence (47 at risk). Solid line: Kaplan-Meier estimate; dotted lines: 95% Confidence Limits.

tory of seizures appeared to lower the overall recurrence rate compared with those with a family history that seize at a lower temperature.

Risk score

A composite risk score was calculated for each child on the basis of the presence of each of the five variables in the final multivariate model for the risk of any seizure recur-

Table 4.1.2. Weights for risk factors for at least one recurrence, and for ≥ 3 recurrences retained in multivariate Cox regression model. Risk level for four hypothetical children (A, B, C and D) with (+) and without (-) factors.

Factor[*]	*Weight*[†] *for any recurrence*	*≥ 3 recurrences*	*A*	*B*	*C*	*D*
Age ≥ 30 months	- 0.8	- 1.2	–	–	–	+
Family history						
unprovoked	+ 1.2	+ 1.6	–	–	–	+
febrile seizure	+ 1.3	+ 1.1	–	–	+	–
Initial seizure						
multiple	+ 0.8	0	–	–	+	–
temperature ≥ 40,0°C.	- 0.7	- 0.8	–	+	–	+
Risk-score for any recurrence			0	- 0.7	2.1	- 0.3
Risk of any recurrence[‡]			*Medium*	*Low*	*High*	*Low*
Risk-score for ≥ 3 recurrences			0	- 0.8	1.1	-0.4
Risk of ≥ 3 recurrences[‡]			*High*	*Low*	*High*	*Low*

[*] Indicator variables coded as 0 = attribute absent, 1 = attribute present;
[†] Regression coefficient from multivariate Cox model for at least one and for ≥3 recurrences;
[‡] Categories defined in text.

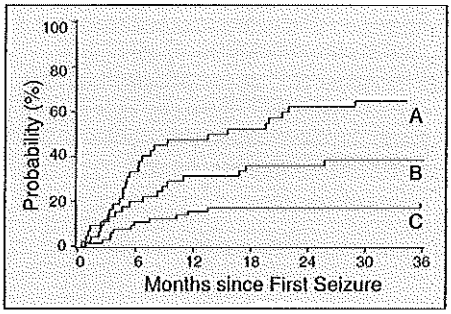


Figure 4.1.2. Probability of seizure recurrence according to risk score: A) high risk (N= 42), B) medium risk (N= 47), C) low risk (N= 66). Kaplan-Meier Estimates.

4.1.2

rence. Weights and coding are given in Table 4.1.2, with a calculated risk score for 4 hypothetical children. Patients were divided into 3 risk groups: 'low' (n = 66), 'medium' (n = 47) and 'high' (n = 42). Figure 4.1.2 shows the Kaplan-Meier curves for children at these three levels of composite risk of first recurrence. At 12 months after the initial febrile seizure there is a cumulative recurrence rate of 48% for the 'high' risk group as opposed to a 15% for the group at 'low' risk. There is an obvious difference in recurrence pattern between groups ($p = 0.01$). Only four of 45 children in the low-risk group developed three recurrences.

Similar scores were calculated from the results of the predictive model for the occurrence of 3 or more subsequent febrile seizures. Patients were divided according to score values into 2 risk groups: 116 low risk and 39 high risk. Three or more recurrences developed in 13 (11%) children in the 'low' risk group and in 14 (36%) children in the 'high' risk group. Using this risk score to address the risk of multiple recurrences, the risk of any seizure recurrence for the whole cohort was assessed and provided a good differentiation between children with a high and low first-year risk of recurrence. The observed cumulative recurrence rate was 38% and 14% after 6 months, and 48% and 23% after 12 months for high- and low-risk children, respectively; all differences were statistically significant.

DISCUSSION

The aim of the present study was to determine the influence of potential risk factors on the seizure recurrence rate, according to the presence or absence of other risk factors. Also studied were the course and outcome of children *after* a first recurrent seizure and the evolution of the recurrence risk over time since the last seizure. We concentrated on predictors of multiple recurrences, since we feel this to be a relevant clinical outcome of febrile seizures. Children at high risk of multiple recurrences may be candidates for continuous prophylactic treatment for some time, while those at risk of just one or two uncomplicated recurrent seizures would probably not need such treatment.

Recurrences

The percentage of all 155 children with at least one and two or more recurrences after the first febrile seizure was 37% and 30%, respectively. This is consistent with the general rates in clinic-based studies reported in Berg's review. [10] The occurrence of three or more subsequent seizures in initially untreated children was 17% (27/155). Only one other clinic-based study reports a figure—35%—for this separate clinical end point. [6] Population-based studies have reported rates of 4.1% to 9%. [1,3] Non-febrile seizures occurred in the present study in 3% of children; previous clinic-based studies with varying follow-up time have reported rates of 2.6% to 76.9%. [18] In the present study there were no neurological sequelae from recurrent seizures and only one child had a complex recurrence. However, children with aberrant previous neurological status and acquired sequelae at the initial febrile seizure—a postulated main predictor of epilepsy—[1] were excluded.

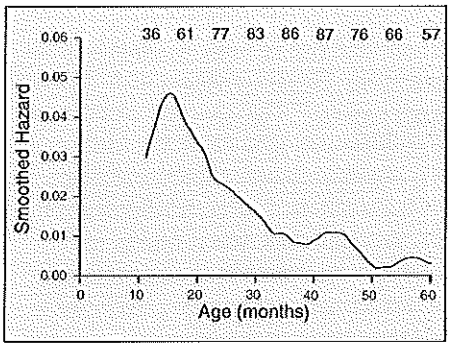
Risk Factors

First-degree family history of any type of seizure was associated with both single and multiple recurrences (Table 4.1.1): this is consistent with other studies. [10] A body temperature ≥ 40.0° C at the initial seizure appeared to be associated with a lower risk, as was an age of ≥ 30 months. The association between elevated temperature and recurrence risk has also been reported by El-Radhi and coworkers. [4,7] A high body temperature at the initial seizure seems to modify the effect of a positive family history of seizures by lowering the recurrence rate. These findings are compatible with a model of decreased seizure threshold at a certain age, which, as suggested by Aicardi, [8] may be mainly genetically determined. A long or focal initial seizure, and even status epilepticus without neurological sequelae, were not associated with an increased risk of further febrile seizures. Again, these findings are consistent with those in Berg's review. [10]

Since several factors appear to act together on the risk of recurrent seizures—sometimes in opposite ways—a composite recurrence risk 'score' was assigned to each patient. Using all relevant factors in combination, it was possible retrospectively to identify subgroups of children with a one-year recurrence risk as low as 15% (high temperature, no risk factors) and as high as 48% (low temperature, family history or multiple initial seizure) (see Table 4.1.2 and Figure 4.1.2). In addition, groups of children at high and low risk for frequent recurrences could be identified, with one quarter of all children (39) being at an three-fold risk (36% vs. 11%).

Recurrence hazard over time, the role of age

Of great relevance to the decision to start (and stop) continuous prophylaxis is the finding of a rapidly declining overall recurrence hazard during the three to six months after the previous seizure (Figure 4.1.1); this decline seems to be even greater among high risk children (see Figure 4.1.2). In light of the recently described effects of long-term phenobarbital prophylaxis on children's cognitive development, [12] we feel that only short term treatment—if any—after a first febrile seizure in children with several risk factors would be justified.



4.1.3

Figure 4.1.3. Smoothed recurrence hazard (in number of recurrences per person-month of follow up) after first febrile seizure as a function of attained age. Numbers at top indicate number of children at risk at each age.

The effect of age was studied in more detail. In contrast to previous reports, [10] children whose initial febrile seizure was before one year of age were not at higher risk of recurrent seizures than those whose age at onset was between 12 and 30 months (see Table 4.1.1). On the other hand, children with multiple recurrences had their first and second febrile seizures at younger ages than those with none, one or two recurrences. However, the time interval between seizures—often used as a clinical basis on which to start anticonvulsant prophylaxis treatment when the interval is short (e.g., less than three or six months)—did not provide any additional information.

We hypothesized that there is a critical age-period in which children with febrile seizures are most vulnerable to recurrent seizures. To determine this age-period, we estimated the recurrence hazard rate—defined as number of recurrences per unit person-time of follow-up—as a function of the attained age for all children in the study. [17] In this analysis the recurrence hazard rate is calculated for each age-group at risk for further seizures, containing only children who had their first febrile seizure before that particular age and had not (yet) had a recurrence. Thus, each child enters the risk set at its age at seizure onset and leaves the set at higher age, either through the occurrence of a subsequent seizure or at the end of follow-up. Using the technique described by Thaler a 'smoothed' recurrence hazard function was constructed (Figure 4.1.3). [19]

The recurrence hazard was highest between 12 and 24 months of age, after which it dropped to a much lower level beyond the ages of 30 to 36 months. The recurrence hazard curve is very similar to recently published age-at-onset distribution curves , [20–22] and is consistent with the theory of increased seizure susceptibility during particular stages of cerebral development during the second year of life. [20] It would be interesting to examine the effect of risk factors on this age-based recurrence hazard; however, in the present study too little data were available for stratification.

It is likely that, in addition to the factors studied, other factors during the period after the initial febrile seizure, such as the number of febrile episodes, [23] parental management of fever, and the type of infections, [24–26] may influence the recurrence risk. To improve our understanding of seizure recurrence in various risk groups these factors need to be further studied.

The results of the present analysis are relevant to decisions about preventive anticonvulsive treatment after a first febrile seizure. The decision is based on inconvenience and side-effects of prolonged treatment with antiepileptic drugs against the risk of multiple recurrences, with possible subsequent neurologic impairment. Our finding that the risk of recurrent seizures is highest between 12 and 24 months of age and declines rapidly after six months from the previous seizure suggests that any prophylactic treatment after a first febrile seizure should be restricted in duration and recommended only to children with multiple risk factors. Since most follow-up studies have shown that (first) recurrent seizures are not threatening, it may even be advocated that 'high risk' children be treated only after the first recurrence. In order to prevent lengthy recurrences it seems to be of greater importance to counsel the parents properly, and to instruct them how to manage fever and recurrent seizures by administration of rapidly acting anticonvulsants, such as a diazepam solution by rectum.

CONCLUSIONS

1 The main findings of the present study are that the combined predictive value of age at onset, first degree family history of seizures of any kind, nature of the first seizure (single or multiple) and degree of fever at first febrile seizure (more or less than 40° C) for both single and multiple recurrences is superior to that of single variables.

2 The child's age at each subsequent febrile seizure has predictive value for further seizures: the younger the child at the second and third seizures, the higher the likelihood of further recurrences. The hazard of recurrence after a first febrile seizure is highest between the ages of 12 and 24 months. In contrast, time between seizures varies little between children with or without ≥ 3 recurrences. Therefore, when assessing the prognosis, it seems more appropriate to consider only the age of the child at each recurrent seizure.

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4.2 Risk factors for seizure recurrence in children with febrile seizures—a pooled analysis of individual patient data from five studies

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INTRODUCTION

Several population-based and clinic-based follow-up studies have addressed the course after an initial febrile seizure in otherwise healthy children. [1–8] In general, children with febrile seizures have a good long-term prognosis, although in clinic-based series an increased risk of subsequent epilepsy has been found. [9] The primary 'sequela' of a febrile seizure seems to be a high risk of seizures during subsequent febrile episodes. Most studies have limited their follow-up to the first recurrence, and the relation between risk factors and the rate of recurrent seizures has been studied mainly by univariate analyses. These results may have been confounded by other factors influencing the recurrence rate (i.e., factors related to both the presence of a risk factor and the outcome). Furthermore, most studies have not provided detailed information on the prior neurologic status of the subjects, which has been weakly associated with recurrence in some studies.

Previous studies have reported that an increased risk of recurrence is associated with young age at onset, [1,3,7,8] a history of afebrile seizures, [1] or of seizures of any kind in a first degree family member, [3,5,8] an initial complex seizure (partial, prolonged or multiple), [2] and a relatively low body temperature at the time of the first febrile seizure. [4,5,8] A recent meta-analysis attempted to summarize the findings from 14 published studies. [10] Except for age at onset, no single risk factor consistently identified children at high or low risk of recurrent seizures. The authors recognized that because of the lack of access to individual patient data, their analytic technique did not allow them to study the influence of confounding factors.

The objective of this analysis was to assess the following: (1) the relationship between age and the recurrence of seizures after a first, second, and third febrile seizure in previously healthy children, and (2) the relation between the postulated risk factors and frequent recurrence of seizures and the occurrence of complex seizures (i.e., partial, prolonged, or multiple), with control for confounding factors.

We pooled data from individual patients from five follow-up studies that used similar definitions of febrile seizures and risk factors. We excluded children with neurologic

abnormality before or soon after the first febrile seizure, and children treated prophylactically who had regular monitoring.

METHODS

Selection of studies and patients

We selected those cohort studies that (1) were published in the years 1978–1992, (2) used the same definition of febrile seizures and risk factors, (3) contained information on risk factors and on the number, timing, and type of recurrence, and (4) had continued the follow-up after recurrent seizures. Six studies were identified. [1–6] The original authors of five of these agreed to make individual patient data available. We distinguished two types of studies: population-based, [1,2] and clinic-based. [3–5]

All studies selected had used the definition of febrile seizures adopted at the 1980 National Institutes of Health Consensus meeting. [11] This definition excludes children with a history of non-febrile seizures or with intracranial infection or another defined cause for the seizure. For the purpose of our analysis, children with neurologic abnormality before the first febrile seizure, such as cerebral palsy, mental retardation, and developmental delay, were excluded. Those who had received monitored prophylactic treatment, whether continuous or intermittent, with regular visits to the clinic were also excluded. Fever was defined as a temperature of $\geq 38.0°$ C, [1,2,4] or $\geq 38.5°$ C. [3,5] Study 1 comprised 1,821 children with febrile seizures. Of these, 1,706 (94%) were followed until the age of seven years and were included in the original report. From this study 356 subjects with pre-existing neurologic or developmental abnormalities were excluded for this analysis. Children who had received unmonitored anticonvulsive treatment for 1 month or more (13% in study 1) were not excluded because such treatment is ineffective. [12,13] Study 2 comprised 687 children without pre-existing neurologic abnormality. These children were followed for at least 4 years and up to 25 years until the occurrence of an unprovoked seizure (32 subjects), death (5 subjects), migration from the study area (110 subjects less than 5 years of age) or study termination (remainder). Study 3 was a randomized trial of 289 children; of these, 156 were excluded (152 because they were assigned to the prophylactic treatment group, 4 because of neurologic abnormalities). Ninety percent were followed for at least three months and 68% for at least 18 months. Study 4 comprised 171 children with first febrile seizures who were untreated, had no neurologic abnormality, and were followed for at least 27 months. Study 5 comprised 161 previously normal children with first febrile seizures; six were lost to follow-up and the remaining 155 were followed for at least 30 months.

Outcome events and risk factors

We defined outcome events as any recurrence of a febrile seizure, frequent (≥ 3) recurrent febrile seizures, or occurrence of a complex (partial, prolonged, or multiple) seizure.

We considered three categories of risk factors: (1) a history of febrile and nonfebrile seizures in first degree relatives; (2) the clinical features of the initial febrile seizure,

defined as 'multiple' if they recurred within 24 hours, 'partial' if any focal feature (including Todd paresis) had been present, and 'prolonged' if they had lasted over 15 minutes; and (3) the child's temperature, which, with one exception (1), was available in all studies. In the clinic-based studies (3-5) the temperature had been measured rectally in the emergency department by an attending nurse within 1 hour of the seizure. Only one of two population-based studies provided similar data on temperature (2); less frequently it was taken at home visits. The exact value was considered missing if the temperature was reported only by the parents. A cutoff value of 40.0° C was chosen to differentiate between high and low temperatures.

Statistical analysis: recurrent seizures

We distinguished between the cumulative risk of recurrence after a certain follow-up period and the immediate recurrence risk by the use of the terms 'probability' and 'hazard', respectively. Hazard was defined as the number of recurrences per child-month of follow-up.

We estimated the probability of recurrence using the Kaplan-Meier product limit method, [14] with 95% confidence intervals (CI). [15] We evaluated recurrence hazard as a function of attained age and the other three risk factors cited above. We calculated this hazard for each age group, including only children who had had their first febrile seizure before that particular age and had not yet had a recurrence. Thus, each child entered the set of subjects at risk at the age of the first febrile seizure, and left the set either because of a subsequent seizure or at the end of follow-up. [16]

We used Cox multivariate proportional hazard models to examine the relation of the risk factors to the probability of subsequent seizures. [17] The validity of this proportionality was assessed for all risk factors. [18] We compared children with and without a certain factor, and calculated hazard ratios and their 95% confidence intervals 'adjusted' for other risk factors from the factors' regression coefficients and their standard errors. (By definition, a factor with a ratio > 1 is associated with an increased risk of recurrent seizures; conversely, a factor with a ratio < 1 is associated with a decreased risk.) By means of a stepwise procedure, we eliminated risk factors from the multivariate model. In the final model we retained only those factors with regression coefficients with p values < 0.05. [19] Because we had no information regarding the child's temperature at the first seizure for one large study (study 1), we introduced an 'indicator of missingness' in all multivariate analyses, which was evaluated together with the temperature variable. [19]

We used the same approach to assess the natural history of recurrent febrile seizures. We first analyzed the data for children after an initial recurrence and then after a second one. This was done as a function of attained age (i.e., age at previous seizure plus time since) together with the risk factors.

The recurrence hazards after the initial febrile seizure, after a first recurrence and after a second recurrence were compared and evaluated for proportionality. The association of risk factors with recurrence within these 3 groups was also compared, and thereafter the final analysis was performed; the latter assessed the influence of previous recurrent seizures against all other risk factors. In this analysis the risk of the next seizure was

Table 4.2.1. Characteristics and prevalence of risk factors in studies included.

	All population based	*All clinic-based*
Study characteristics		
First author		
Study base		
Median follow-up time (months)		
Number of children	2037	459
No. (%) with any recurrence	646 (32)	163 (36)
No. (%) with ≥ 3 recurrences	138 (7)	47 (10)
No. (%) with 'complex' recurrence	98 (7)†	24 (5)
Prevalence of risk factors		
Gender		
female (%)	45	43
male (%)	55	57
Age at onset (months)		
median (range)	18 (2–135)	17 (4–79)
< 12 (%)	23	20
12–30 (%)	55	64
≥ 30 (%)	22	16
Family seizure history ‡		
none (%)	72	72
either febrile or unprovoked (%)	28	28
febrile (%)	18	24
unprovoked (%)	10	4
both febrile and unprovoked (%)	4	5
Clinical features of initial febrile seizure (FS)		
duration ≤ 15 minutes (%)	94	93
duration > 15 minutes (%)	6	7
generalized (%)	96	97
partial (%)	4	3
single (%)	88	87
multiple (%)	12	13
any 'complex' feature (%)	20	21
temperature		
median in degrees Celsius	39.8	39.6
< 40.0°C (%)	52	63
≥ 40.0°C (%)	48	37
Mean No. of risk factors ††	1.09	1.15

* Not available; † number of complex recurrences in study (2) is unknown, this number is the number in study (1); ‡ only first degree family; †† family history was coded in mutual exclusive categories, the presence of unprovoked seizures precluding the presence of febrile seizures.

Study 1	*Study 2*	*Study 3*	*Study 4*	*Study 5*
Nelson[1]	Annegers[2]	Knudsen[3]	El Radhi[4]	Offringa[5]
Population	Population	Clinic	Clinic	Clinic
63	178	18.5	48	40
1350	687	133	171	155
439 (33)	207 (30)	46 (35)	59 (35)	58 (37)
110 (8)	28 (4)	11 (8)	10 (6)	26 (17)
98 (7)	.	14 (11)	8 (5)	2 (1)
47	41	42	46	42
53	59	58	54	58
19 (2–84)	18 (2–135)	17 (4–79)	16 (6–52)	18 (6–54)
23	21	23	22	16
52	62	58	67	64
25	17	19	11	20
74	70	74	61	82
26	30	26	39	18
15	23	20	37	13
11	7	6	2	5
5	2	5	..	..
95	92	96	95	88
5	8	4	5	12
97	95	97	98	95
3	5	3	2	5
89	86	86	91	84
11	14	14	9	16
18	22	18	14	30
.	39.8	39.5	39.8	39.7
.	52	77	52	62
.	48	23	48	38
1.08	1.11	1.29	1.08	1.12

[††] Risk factors considered: a family history of FS, a history of unprovoked seizures, a partial, prolonged or multiple initial FS, and a body temperature < 40.0° C at the first FS. Theoretical maximum number of risk factors is 6.

determined by the child's attained age, the presence of risk factors and a history of previous recurrences.

Statistical analysis: occurrence of complex seizures

We assessed the relationship between risk factors and subsequent complex seizures by calculating relative risks and its 95% confidence intervals from 2 × 2 tables, which relate the presence or absence of a risk factor to complex seizures. [20] The independent relation between risk factors and the occurrence of complex seizures was assessed in a stepwise multivariate logistic regression model. [20] Thus, we adjusted each risk factors' association with a subsequent complex seizure for the presence of other factors.

Statistical analysis: pooling of data

To check the consistency among studies, we first analyzed the relations of risk factors to the outcomes for each study separately. After a test of homogeneity we pooled the data. The study source was accounted for and evaluated as an indicator variable. The final Cox model (recurrent seizures) and logistic regression model (subsequent complex seizures) were fitted to the data of each individual study, and the results were compared with the pooled result.

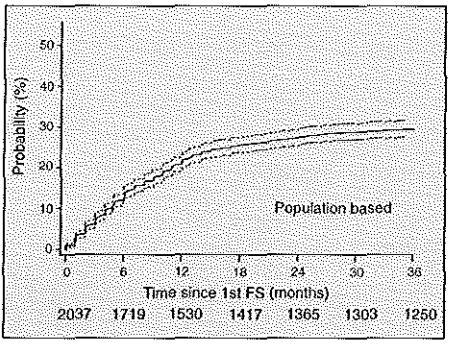
Univariate statistics, Kaplan-Meier product limit estimators, non-parametric hazard estimates, and logistic regression coefficients (LOGIST procedure) were calculated with the SAS-PC statistical package (SAS Institute Inc., Cary, NC). For the proportional hazard models the BMDP package (BMDP Statistical Software, Inc., Los Angeles, CA) and the EGRET package (Statistics and Epidemiology Research Corp., Seattle, WA) were used.

RESULTS

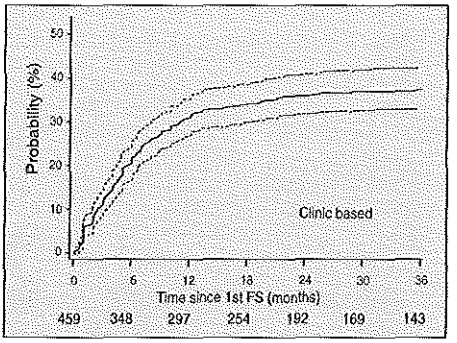
Study population and prevalence of risk factors at baseline

Table 4.2.1 summarizes the characteristics of the 2,496 children with febrile seizures included in this analysis. The two population-based studies (1,2) contributed more than four times the number of cases of the joint clinic-based studies (3-5) and had far longer follow-up times. Overall recurrence rates varied between 30% and 37%; rates of ≥ 3 recurrent seizures were 4% and 8% for the population-based studies, and 6%, 8%, and 17% for the clinic-based studies. On average, 7% of 1,809 children at risk (1, 3-5) had a subsequent complex seizure; no data on such seizures were available in study 2.

Male/female ratios were similar in all studies, with a slight predominance of boys (Table 4.2.1). Median age at onset varied little, but the population-based studies had more children aged ≥ 30 months at onset than in the three clinic-based studies. The latter had a lower prevalence of a history of unprovoked seizures in a first degree family member, but the rate of family history of febrile seizure and the presence of complex features during the first febrile seizure were similar in all studies. Median body temperature at the time of evaluation was approximately 39.7° C in all four studies which doc-



4.2.1a



4.2.1b

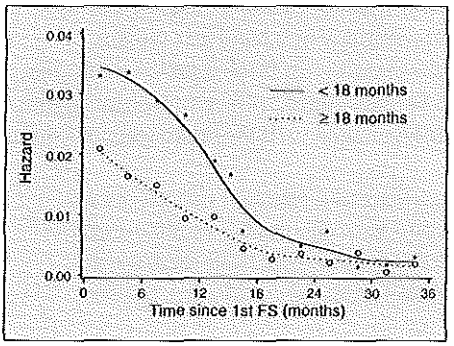
Figure 4.2.1. Probability of at least one recurrent seizure after initial febrile seizure. Pooled population-based and pooled clinic-based studies. Solid line: Kaplan-Meier estimate; dotted lines: 95% confidence limits. Bottom: number of children at risk at each stage during follow-up.

umented this feature. The average temperature values were lowest in study 3, which contained fewer children with temperatures ≥ 40° C.

The overall prevalence of six risk factors at issue (i.e., a family history of febrile or nonfebrile seizures; a partial, prolonged or multiple initial seizure; and a body temperature < 40.0° C at the first febrile seizure) was similar in all included studies, with a highest mean number of risk factors (namely 1.3) in study 3. Pooling of the clinic-based studies showed a mean of 0.06 more risk factors than in the pooled population-based studies. Thus, no major difference in prevalence of risk factors existed between clinic-based and population-based studies.

Single recurrence hazard and risk factors

Figure 4.2.1 shows the Kaplan-Meier estimates of the probability of any recurrence, with their 95% confidence bands for both study types. After three years the probability was 30% in the pooled population-based studies (95% CI 28 to 32%) compared with



4.2.2

Figure 4.2.2. Smoothed recurrence hazard (in number of recurrences per child-month of follow-up) with time since the initial febrile seizure, according to age at onset.

Table 4.2.2. Relation of risk factors to recurrence according to the number of previous seizures.

Risk factor	*After a first febrile seizure* *N*	*% rec*	*HR*	*(95% CI)*
Total	2496	32		
Gender				
Male	1384	33	1.01	0.87–1.18
Female	1112	31	r.c.	
Family History				
Febrile seizures	473	43	1.49	1.25–1.77*
Unprovoked	211	37	1.34	1.04–1.73*
Neither	1812	29	r.c.	
Initial seizure				
Duration > 15 min.	160	33	0.89	0.66–1.20
Duration ≤ 15 min.	2336	32	r.c.	
Partial	91	34	0.86	0.58–1.28
Generalized	2405	32	r.c.	
Multiple	308	40	1.26	1.03–1.54*
Single	2188	31	r.c.	
Temp. < 40.0°C†	610	36	1.89	1.47–2.38*
Temp. ≥ 40.0°C†	464	24	r.c.	

rec recurrence. r.c. reference category. HR Hazard Ratio.
Results from Cox analyses based on attained age. Hazard ratios (HR, with 95% CI) adjusted for the presence of other factors are presented.

38% in the clinic-based studies (95% CI 33 to 43%). Most of these first recurrences occurred during the 12 months after the initial febrile seizure.

Figure 4.2.2 depicts the recurrence hazard with time for two different age-at-onset-groups: this closely approximated the monthly probability of a recurrent seizure. Hazards were highest in the first 12 months after a seizure. In those aged < 18 months at onset, the hazard remained high longer than for those aged ≥ 18 months: during the first 6 to 18 months, it was twice as high for children aged < 18 months compared with those aged ≥ 18 months.

Figure 4.2.3 shows the hazard of seizure recurrence as a function of attained age. After the initial febrile seizure (curve A) the hazard was highest (2.5 to 3.0 events per 100 child-months of follow-up) between age 12 and 24 months, and the hazard decreased to less than 0.5 events per 100 child-months of follow-up after age 36

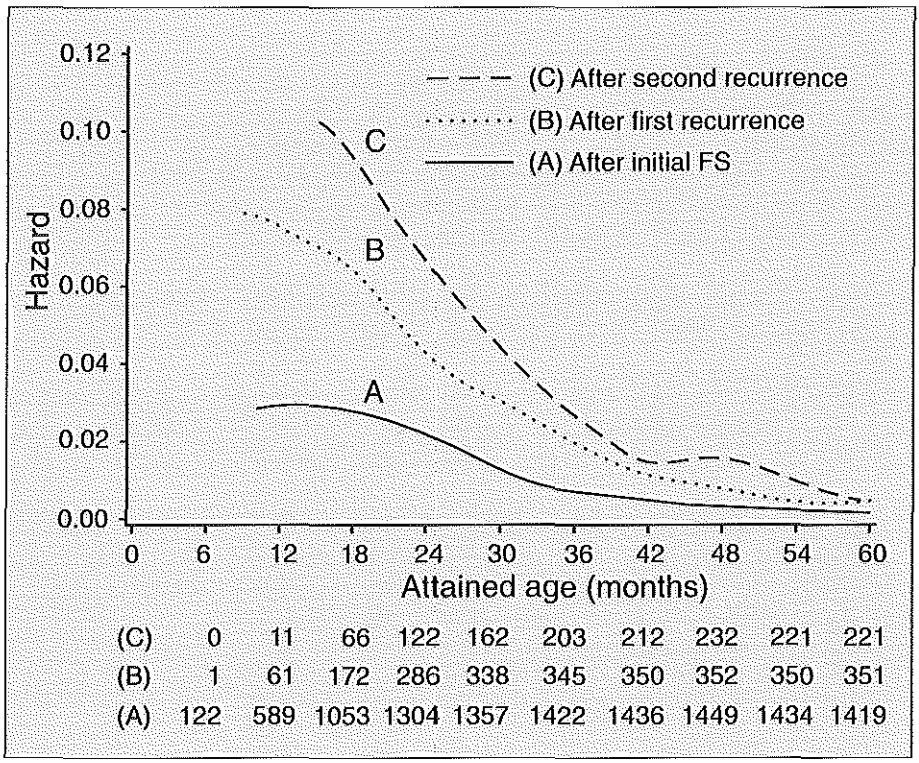
After a first recurrence				*After a second recurrence*			
N	*% rec*	*HR*	*(95% CI)*	*N*	*% rec*	*HR*	*(95% CI)*
809	47			378	49		
460	49	1.18	0.94–1.48	226	50	0.86	0.60–1.24
349	44	r.c.		152	48	r.c.	
201	49	1.32	1.01–1.71*	98	55	1.55	1.02–2.34*
79	47	1.29	0.89–1.87	37	57	1.96	1.14–3.37*
529	38	r.c.		243	38	r.c.	
52	50	0.86	0.54–1.34	26	62	1.32	0.67–2.59
757	46	r.c.		352	48	r.c.	
31	52	1.30	0.74–2.30	16	63	1.02	0.40–2.56
778	47	r.c.		362	48	r.c.	
123	45	0.80	0.58–1.11	55	58	1.22	0.76–1.95
686	47	r.c.		323	47	r.c.	
218	50	1.52	1.02–2.27*	108	50	1.79	0.74–4.35
113	34	r.c.		38	34	r.c.	

* statistically significant factors retained after stepwise elimination from the multivariate Cox model.
† after exclusion of all subjects from study 1, temperature values were missing in 72 of the remaining 1146 subjects at risk.

months. For instance, at age 18 months the hazard of a recurrence in the next month was 3 per 100 versus a hazard of 0.2 per 100 at age 48 months.

We evaluated the risk factors with Cox models formulated on the basis of this attained-age hazard. The validity of the proportionality assumption was satisfactory for all risk factors, and their influence homogeneous for the five studies. Hence we report only the results of the pooled analyses.

A family history of seizures, either febrile or nonfebrile, was associated with an increased hazard of at least one recurrence after the initial febrile seizure, as was a 'multiple' initial seizure (Table 4.2.2). Children with temperature < 40.0° C had twice the risk of recurrences compared with those with higher temperatures. When temperature was eliminated from the model, the hazard ratios for the other risk factors were similar. Thus, the temperature variable added extra information and did not confound the other factors' relation to recurrence.



4.2.3

Figure 4.2.3. Smoothed recurrence hazard (in number of recurrences per child-month of follow-up) as a function of attained age. Numbers at bottom indicate children at risk at each age. Note that children are joining the group-at-risk over time as they have their first FS and have not yet had a recurrence. After 48 months the number at risk of a recurrence declines as the children with recurrences (or censoring) outnumber new entries.

Introducing the study population source (i.e., whether clinic- or population-based) into the multivariate model did not change the regression coefficients of risk factors. Nevertheless, in clinic-based studies there was a 1.4-fold increased risk of recurrence (95% CI 1.2 to 1.6). This increase cannot be explained by confounding by other risk factors.

Multiple recurrences and risk factors

Figure 4.2.3 shows the hazard of further recurrences after a first and a second recurrence. By age 24 months 286 children had had one recurrence but had not had a second recurrence. By this same age, 122 other children had had two recurrences but had not had further seizures. The hazards after recurrences were again highest between the

ages of 12 and 24 months; after a first and a second recurrence, the risk of further recurrences was two and three times higher, respectively. The hazards after a second and a third febrile seizure seemed to be proportional to the hazard of a recurrence after the first febrile seizure.

To assess the relation of the risk factors to the hazard of further recurrences after a first and a second recurrent seizure, we used the same approach as described for risk factor assessment for a first recurrence. Table 4.2.2 summarizes the findings for children at risk of a second and a third recurrence. After a first recurrent seizure the associations of risk factors with the next recurrence were similar. However, only a family history of febrile seizures and a relatively low temperature at the initial febrile seizure were retained in the Cox model after stepwise exclusion (Table 4.2.2). After a second recurrent seizure, family history of febrile and unprovoked seizures was associated with further seizures (Table 4.2.2). Introduction of a clinic-based or population-based study indicator into these two multivariate models resulted in unchanged coefficients for the risk factors, and indicated a 1.2- to 1.4-fold increase in recurrence hazard for children in the clinic-based studies.

Table 4.2.3 summarizes the results of the final analysis. A family history of febrile or unprovoked seizures, the temperature at the first febrile seizure, and a history of recurrent seizures were all relevant factors. A recent seizure (< 6 months previously) was also important. During the first 6 months after a febrile seizure (at any age) the recurrence hazard was 1.7 times higher than thereafter. The recurrence hazard for children in the clinic-based studies was 1.6 times higher (95% CI 1.3 to 1.9) than that in the population-based studies.

To check the consistency of the results, we fitted the final Cox model to the data from each separate study and derived hazard ratios and 95% CIs for all risk factors. We

Table 4.2.3. Relations of risk factors and seizure history to recurrence after any febrile seizure (FS).

	Hazard ratio	*95% CI*
Family history of any type of seizures	1.42	1.26–1.59
Initial FS temperature < 40.0°C	1.54	1.25–1.89
One previous recurrence	1.98	1.72–2.27
Two previous recurrences	2.59	2.20–3.04
Time lapse since previous seizure < 6 months	1.68	1.47–1.92

Results from Cox analysis based on attained age, after stepwise elimination from the multivariate model. Risk factors considered: a family history of FS or unprovoked seizures, a partial, prolonged or multiple initial FS, a body temperature < 40.0°C at the first FS, number of previous seizures, and the occurrence of a seizure < 6 months previously.

found that the risk factors' relations with recurrence were consistent throughout the five studies.

Subsequent complex seizures and their risk factors

Information on the occurrence of complex seizures at any time during follow-up was not available in study 2; hence all 687 children from this study were excluded from the

Table 4.2.4. Relation of risk factors to complex recurrences.

Factor	*At risk No.*	*Complex recurrences %*	*Univariate analysis R.R. 95% CI*	*Multivariate model R.R. 95% CI*
Gender				
male	981	7.4	1.23 0.87–1.74	n.s.
female	828	6.0	r.c.	
Age at FS onset (months)				
< 12	402	11.1	1.84 1.27–2.67	2.10 1.42–3.10
12–30	996	6.0	r.c.	
≥ 30	411	4.2	0.72 0.43–1.21	n.s.
Family seizure history				
none	1328	6.1	r.c.	
febrile	395	8.3	1.17 0.75–1.83	n.s.
unprovoked	163	11.0	1.78 1.10–2.90	1.80 1.04–3.11
both febrile and unprovoked	77	12.9	1.99 1.08–3.64	n.s.
either febrile or unprovoked	481	8.5	1.38 0.96–1.97	n.s.
Clinical features initial seizure				
duration > 15 minutes	106	3.7	0.54 0.20–1.44	n.s.
duration ≤ 15 minutes	1703	6.9	r.c.	
partial	58	13.7	2.10 1.07–4.09	2.35 1.08–5.10
generalized	1751	6.6	r.c.	
multiple	212	4.7	0.66 0.35–1.25	n.s.
single	1597	7.1	r.c.	
any 'complex' feature	343	6.4	0.93 0.59–1.45	n.s.
< 40.0°C *	288	6.6	r.c.	
≥ 40.0°C *	171	2.9	0.44 0.16–1.16	n.s.

R.R. Relative risk expressed as percentage of complex recurrences when the attribute is present divided by percentage of complex recurrences when the attribute is absent (i.e., in the reference category).
n.s. not selected in multivariate logistic regression model.
r.c. reference category.
* analysis of temperature only for studies 2,4, & 5. Effective sample 459, with 24 (5%) complex recurrences.

analyses. In the remaining 1,809 children at risk, 122 (7%) recurrences had complex features. In 64% these recurrences were multiple, in 15% prolonged, and in 7% partial; 15% combined two or three complex features. Only 15% of subsequent complex seizures followed a first complex febrile seizure.

Table 4.2.4 shows the association of risk factors with the occurrence of complex seizures. Age at onset <12 months, a family history of unprovoked seizures, and a partial initial febrile seizure were associated with an increased risk of subsequent complex seizures. These three factors were retained in a multivariate logistic regression model after stepwise elimination. A partial initial febrile seizure had the strongest independent association with subsequent complex seizures (adjusted relative risk 2.35). We found no great difference in occurrence of complex seizures between children from clinic-based and population-based studies (relative risk for subjects in clinic-based study 0.7, 95% CI 0.5 to 1.1).

DISCUSSION

Previous studies have reported the risk of seizure recurrence as cumulative incidence (i.e., the total number of recurrences after a specified period of follow-up) and the association between risk factors and seizure recurrence as risk ratios (i.e., as the ratio of two cumulative incidences). Such measures fail to reflect the changes in the risk with time. Therefore, we have used the concept of the recurrence hazard (the number of recurrences per child-month of follow-up) to describe this risk. Both cumulative incidence and recurrence hazard are affected by loss to follow-up if the reason for this loss is related to seizure recurrence. The studies incorporated into this analysis all followed high proprtions of subjects until the termination of the study. Whether migration, a reason for premature termination in 110 patients in study 2, was related to recurrence in that particular study, is unknown.

We found that the recurrence hazard declined with time, and was highest in the first 6 to 12 months after the initial seizure. Children aged < 18 months at onset had a higher recurrence hazard; moreover, the hazard remained higher for longer, compared with that in children aged > 18 months at onset. Both these findings could be described succinctly by considering the recurrence hazard purely as a function of attained age. Thus, two children of the same age and with similar risk factors have the same recurrence hazard.

With this approach, it might seem that the earlier cited single most powerful indicator of recurrence risk—low age at onset of febrile seizures—is no longer important. This is not true: Age at onset is implicit in the definition of recurrence hazard as a function of attained age. In addition, because the recurrence hazard is high in the second year of life, a child with a first febrile seizure at a low age faces a longer period of increased susceptibility to subsequent seizures.

A second important factor influencing the recurrence hazard, we found, was the child's history of seizures in terms of the number of episodes of febrile seizures experienced. Thus, at any age, the recurrence hazard increased with the number of previous

seizures. Such hazards were roughly proportional: after two febrile seizures the recurrence hazard was twice as high as that in otherwise similar children with only one previous episode. After three or more episodes, the recurrence hazard was 2.5 times higher.

Our recurrence hazard distribution based on attained age corresponds closely with that for febrile seizure age at onset. [21,22] They are consistent with the concept that susceptibility to seizures is increased during the second year of life. Nevertheless, the exact age of highest susceptibility may differ among individuals. We allowed for such variability by including a 'seizure recency indicator' in our multivariate model. In otherwise similar children of the same age, the recurrence hazard was 1.7 times higher if the previous seizure had occurred less than six months earlier.

With regard to the other risk factors, only a family history of seizures and the child's temperature at the initial seizure were associated with recurrent seizures. The former factor has been reported in several studies. [1,3,5,8] The latter was first reported in a small study, [4] but we have now confirmed its importance in our larger dataset. Although the exact time and place of temperature measurement were not known for every case in the study, the results for the separate and pooled clinic-based studies all indicate similar findings. Moreover, we found that a relative low temperature at the initial febrile seizure (i.e., < 40.0° C) remained associated with further seizures after a first recurrent seizure. Such findings fit nicely into a concept of a genetically determined threshold of seizures during a certain age period. [23] Nevertheless, the temperature measured at any time after the seizure may be a poor reflection of the actual temperature at the time of the seizure. Instead, it might be an indicator of other factors related to the episode, such as time delay in taking the temperature, the use of antipyretic agents, or how the child was clothed. There are no data regarding the exact body temperature in children with a febrile seizure, either at the beginning of the seizure or after one, two or three hours. We believe that temperatures measured more than an hour afterwards or calculated historically should be rejected as invalid. Certainly, even those temperatures regarded as valid (as in our case) should be used with caution in planning strategies for prevention of recurrence.

Complex features of the initial febrile seizure have been reported to imply an increased risk of recurrence. [2,3,13,24] Our examination of the relation of these features to the recurrence hazard showed that only a multiple initial seizure was associated with an increase in recurrence. Prolonged or partial initial seizures did not increase the recurrence hazard provided they were not associated with permanent alterations in neurologic function. Extensive testing for an interaction between the complex factors and the major risk factors (age, family history, temperature) showed no increased recurrence risk in subgroups of children who have both complex and major risk factors.

So far, no risk factors for the subsequent occurrence of complex seizures have been identified. Because we had no information on the time to such a recurrence, we chose the multiple logistic regression model to examine any relation of risk factors to complex recurrences, using their cumulative incidence after a follow-up of two years from the initial febrile seizure. Complex seizures occurred in 7% of cases, usually as multiple febrile seizures. Prolonged recurrences and recurrences with combinations of complex

features occurred in only 2%. These figures can be put into perspective: of all the children in the four studies detailing on subsequent complex seizures (n = 1,809), 343 (19%) had one or more complex features at their first febrile seizure; therefore, most complex febrile seizures seem to be initial febrile seizures.

Factors that we found to have an independent relation to the occurrence of complex seizures were a partial initial seizure, age < 12 months at the first febrile seizure, and a family history of unprovoked seizures. We did not analyze the risk of recurrences for the separate complex features because, even in this large dataset, there were too few focal and long-lasting recurrences. Children with a partial initial seizure are in the minority (3%) but they should be followed with care, especially if they are young.

Our final multivariate models for frequent recurrent seizures showed a 1.6 times higher recurrence hazard for children in clinic-based studies with otherwise similar risk factors. Hence the difference in recurrence rate between clinic- and population-based studies could not be explained by a difference in the known risk factors at the initial febrile seizure. Children in clinic-based studies should be regarded as a subgroup that has been referred for some reason. Recent surveys in England and the Netherlands have shown that general practitioners manage up to 55% of all febrile seizures at home. [25–27] One of these studies indicated that the duration of the seizure, the height of the fever, and the timing of the febrile seizure occurrence during the febrile illness all influenced the general practitioners' decision to refer the child to a specialist. [27]

CONCLUSIONS

We conclude that the risk of subsequent febrile seizures after an initial febrile seizure peaks between the ages of 12 and 24 months, and is further increased when there is a history of febrile or unprovoked seizures in a first-degree family member, and when the temperature at the initial febrile seizure is < 40.0° C. A history of recurrent febrile seizures is an additional risk, especially when the child is younger than 3 years of age. In general, complex features do not increase the risk, but a partial initial febrile seizure carries an increased risk of another complex seizure. Other factors must influence recurrence; these need to be studied to improve our understanding of seizure recurrence.

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4.3 Prediction of seizure recurrence in children with febrile seizures—a validated risk model

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INTRODUCTION

Febrile seizures are the most common neurological problem of childhood and occur in 2% to 4% of all children. [1–3] Of these, 15% to 80% are reported to have recurrent seizures during subsequent febrile episodes. [4–6] The possibility of seizure recurrence, especially frequent seizures or seizures with complex features (i.e., partial, prolonged or multiple) is of concern to both parents and clinicians. Prolonged recurrences (lasting more than 15 minutes) and seizures with complex features carry, conceivably, some risk of persistent neurologic damage. It is therefore useful to identify children at increased risk of frequent and complex recurrences, for they may be candidates for prophylactic measures. On the other hand, knowing that their child is at a relatively low risk of subsequent recurrent seizures might re-assure parents and reduce anxiety.

Several follow up studies of children with a first febrile seizure have been reported during the last decade. In a previous report, [7] we used data from 5 published studies to identify risk factors for recurrent seizures following an initial febrile seizure. [8–12] We found that the child's age is the most dominant determinant of the probability of further seizures. Other risk factors were a positive first degree family history of seizures and a temperature lower than 40.0° C at the initial febrile seizure. In addition to these factors, the number of previously experienced febrile seizures (1, 2, 3 or more) increased the risk of further recurrences.

In the same study, we found that subsequent seizures with complex features are relatively rare and consist mainly of multiple febrile seizures, i.e., re-occurring seizures within 24 hours. [7] In 2% of all children recurrences longer than 15 minutes or with combinations of complex features were observed. Factors that increased the probability of a recurrence with complex features were a partial initial febrile seizure, an age under 12 months at the initial febrile seizure and a family history of unprovoked seizures. [7]

Despite the fact that more insight has been gained in the determinants of recurrent febrile seizures, the recurrence risk for an individual child remains uncertain. Thus far, the influence of risk factors was reported in terms of relative recurrence risk. The absolute risk of seizure recurrence for children with combinations of particular risk factors could not be derived from this information.

Based on the pooled data from 5 follow up studies, [8-12] we describe the development and application of a predictive model that estimates the risk of recurrent febrile seizures for individual children. To this aim, the combined predictive value of the risk factors is used. A separate risk function for the occurrence of seizures with complex features is developed. To asses the robustness of the predictions we use the data from a separate prospective study of febrile seizures. [13]

METHODS

Selection of Studies

The data from five follow up studies were used to develop a prediction model for seizure recurrence. The origin of these data has been described before. [7] The five studies used similar definitions of febrile seizures and contained detailed information on risk factors, timing and type of recurrent seizures. Individual patient data on previously healthy, untreated children were assembled in a single data base, with a total of 2,496 children followed during 13,500 patient-years at risk of recurrent febrile seizures. [7] The individual patient data from a sixth study on 347 children with febrile seizures were used to validate the risk model described below. [13] Table 4.3.1 summarizes the follow up studies that were used for the derivation and validation of the model.

Not all data were used in the present analyses. Children younger than 6 months or older than 5 years at febrile seizure onset, and those with incomplete data on risk factors and events during follow up were excluded. Thus, the size of the dataset that was used for the derivation of the model was reduced from 2,496 to 2,280 children (91%).

Recurrence Hazard and Risk factors

Complete information on the following potential risk factors for recurrence was available for 2,280 children: age at the first febrile seizure, gender, family history of febrile or unprovoked seizures, temperature at the first seizure, and complex features of the first seizure. Complex features were (1) a partial (or focal) seizure as defined according to criteria of the International League against Epilepsy, [14] (2) a prolonged seizure, defined as lasting longer than 15 minutes, and (3) a multiple seizure, recurring within 24 hours. Follow up ranged from 18.5 to 178 months. Outcome events were recurrent febrile seizures up to the age of 5 years. In total, 1,132 recurrence episodes were observed in 728 children.

Conditional independent risk factors for single and frequent recurrences were identified using a multivariate Cox proportional hazards model. [15] This model describes the relationship between risk factors and the recurrence hazard, defined as number of recurrences per child-month of follow up at risk. In the standard approach, the recurrence hazard is estimated as a function of the months elapsed since the previous seizure. In studying the recurrence risk, we found the child's age to be the predominant predictive factor. [7] In the model the hazard was therefore expressed as a function of attained age, and of clinical features available at the initial febrile seizure. Considered were: gender, family history of febrile or unprovoked seizures, degree of fever (<40.0° C or ≥40.0° C)

Table 4.3.1. Characteristics of Studies included in the present analysis.

	Incorporated in Derivation of Predictive Model					*Used for Validation*
Study	*1*	*2*	*3*	*4*	*5*	*6*
First author	Nelson[8]	Annegers[9]	Knudsen[10]	El Radhi[11]	Offringa[12]	Berg[13]
Study base	Pop	Pop	ER	ER	ER	ER
Median follow-up time (months)	63	178	18.5	48	40	24
Children: No. (= 100%)	1350	687	133	171	155	347
% with any recurrence	33	30	35	35	37	27
% with ≥ 3 recurrences	8	4	8	6	17	5
% with complex recurrence	7	NA	11	5	1	13
First degree family seizure history						
% either febrile or unprovoked	26	30	26	39	18	26
% none	74	70	74	61	82	74
Clinical features of initial febrile seizure:						
% duration > 15 minutes	5	8	4	5	12	10
% duration ≤ 15 minutes	95	92	96	95	88	90
% partial	3	5	3	2	5	16
% generalized	97	95	97	98	95	84
% multiple	11	14	14	9	16	15
% single	89	86	86	91	84	85
% more than one complex feature	1	4	2	2	3	7
% temperature < 40.0°C	NA	52	77	52	62	56
% temperature ≥ 40.0°C	NA	48	23	48	38	44

Pop: General population ER: Emergency Room. NA: Not available.

and presence of complex features (i.e., partial, duration > 15 minutes, or multiple seizures within 24 hours) at first seizure. Details of this analysis are given in the Appendix.

All children were followed from the first febrile seizure. After each recurrence, the child was followed for a subsequent one. As described in the previous report, [7] separate analyses were performed for each study, for children with no previous recurrences, with one previous recurrence and with two previous recurrences. These analyses showed that certain risk factors where predictive both for the first and for recurrences. [7] A final parsimonious model, involving all factors that were found to be consistently associated with recurrence was developed. The number of recurrences experienced after the first febrile seizure (i.e., zero, one or two) was represented by two indicator variables. Thus,

for this analysis, the unit of information in the data set was an 'episode at risk' for a subsequent recurrence, rather than a single child. There were 728 first recurrences and 329 second recurrences observed. The data set thus consisted of 3,337 episodes 'at risk' for a subsequent recurrence: 2,280 at risk for a first recurrence, 728 at risk for a second recurrence and the remainder for a third. The risk factors' coefficients were estimated using a Cox model stratified for study source. This analysis allows for different baseline hazards, depending on study specific selection criteria. For all analyses, the proportional hazards assumption was checked as described by Thaler. [16]

Information on the recurrent seizure type (whether simple or complex) was not available in one study. [9] Hence, all 687 children from this study were excluded from the analyses discriminating between simple and complex subsequent seizures.

In the remaining 1,809 children with information on recurrence type, 602 recurrences (33%) including 122 recurrences with complex features (7%) were seen.

Recurrence Risk in Individual Children

Two separate predictive models were developed:

Risk of any recurrent febrile seizure

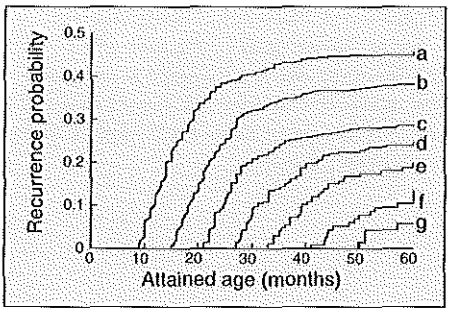
The probability of seizure recurrence within a specified time period for a particular child was calculated with the risk model as described in the Appendix.

Risk of a recurrence with complex features

The risk of a recurrence with complex features was estimated by multiplying the probability of any recurrence by the probability of complex features, given the occurrence of a recurrent seizure. This conditional probability was derived by multiple logistic regression analysis, contrasting complex with simple recurrences among 602 children with at least one seizure recurrence in the subset of 1809 children with information on recurrence type. Risk factors considered were: gender, age at seizure onset, a family history of febrile or unprovoked seizures, a partial, prolonged or multiple initial febrile seizure, and a body temperature below or over 40.0° C at the first febrile seizure. Variables found to be consistently related to complex recurrence were considered risk factors for seizure complexity *given* seizure recurrence, and used for estimation of the absolute risk. Details on the procedures used to derive the predictive model for complex recurrences are given in the Appendix.

Validation of predictions

The accuracy of the predictions was assessed using the original data of a separate follow up study on 347 children with febrile seizures as follows. [13] For reasons described above, the size of this dataset was reduced from 347 to 311 children. In total, 91 first recurrences and 46 second recurrences were observed. The data set thus consisted of 448 episodes at risk for a subsequent recurrence. For each episode at risk, the probability of seizure recurrence after the previous febrile seizure during the available follow up was calculated using the model derived. According to these probabilities, the dataset



4.3.1

Figure 4.3.1. Observed probability of a recurrent febrile seizure with time after a first febrile seizure, by age at onset (a: 9-15; b: 15-21; c: 21-27; d: 27-33; e: 33-41; f: 41-49; and g: > 49 months).

was divided into five quintiles of increasing recurrence risk. The predicted grouped mean recurrence probabilities were compared with the relative recurrence frequency observed in each group.

RESULTS

Crude cumulative probabilities of any recurrent febrile seizures after the initial febrile seizure (i.e., unadjusted for the presence of risk factors) were calculated over time up to the age of 5 years for children in different age at onset groups using Kaplan Meier estimates. The results are presented in Figure 4.3.1.

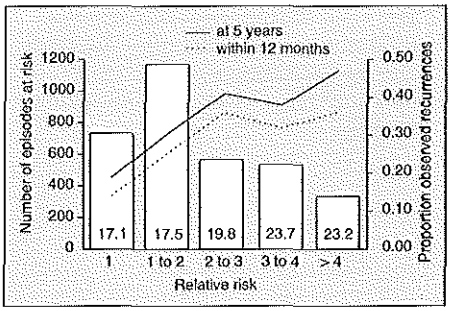
The younger the children were at onset, the higher the probability of any febrile seizure recurrence.

Table 4.3.2 summarizes the results of the risk factor analysis with the multivariate Cox model. For this analysis, the data of 2,280 children with full information on the risk factors and follow up were used. The reported recurrence hazard ratios are 'adjusted' ratios from the full multivariate model, i.e., the values are conditional on the pres-

Table 4.3.2. Relationship of risk factors and febrile seizure recurrence after any seizure.

Risk factor	*Hazard ratio**	*95% CI*
Family history of any type of seizures	1.56	1.38–1.76
Initial febrile seizure temperature < 40.0°C	1.60	1.30–1.97
One previous recurrence	2.02	1.75–2.33
Two previous recurrences	2.40	1.99–2.89

* Results from Cox analysis based on attained age.



4.3.2

Figure 4.3.2. Proportion of recurrent febrile seizures observed within 12 months after a febrile seizure and at the age of 5 years, according to relative recurrence risk, based on risk factors summarized in Table 4.3.2. Median age in each group is given.

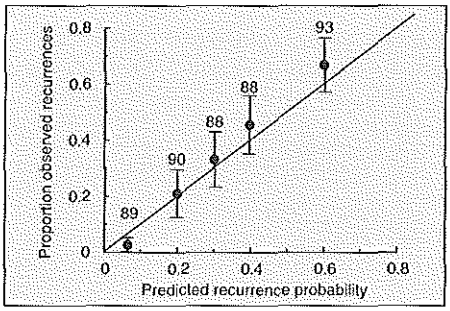
ence of the other risk factors. Age is implicit in this model, which depends on attained age (see Appendix).

A first degree family history of febrile or unprovoked seizures and degree of fever at the initial febrile seizure were consistently associated with seizure recurrence. These were considered risk factors for seizure recurrence and were used in the analyses. In case of recurrent seizures, the number of experienced recurrences were related to the risk of further seizures. Gender and complex features of the initial febrile seizure had no consistent influence on recurrence. It is noted that these hazard ratios differ somewhat from those presented in our previous report, [7] due to the fact that here the reported multivariate model included a factor relating to the recency of the previous seizure (whether it occurred shorter or longer than 6 months before).

The relative recurrence risk for each episode at risk was based on the presence of risk factors. Relative risks ranged from 1 (no risk factors) to 5.98 (all risk factors present). The number episodes at risk in five risk groups and the observed proportions of recurrences within 1 year from the previous febrile seizure and at an age of 5 years are given in Figure 4.3.2. Most episodes (65%) are in the low risk groups (score 1-2). It is noted that the fact that the observed proportion of recurrences seems to go down in the group with relative risks between 3 and 4 is due to the fact that in this dataset children in this group had an on average higher age. Because of this confounding by age the mean ages are given (Figure 4.3.2).

Validation

The results of the validation analysis, which examines the ability to predict probability across all ranges of risk in an independent study, are presented in Figure 4.3.3. The line at 45° represents perfect calibration. There is a slight over-estimation of the recurrence probability in the lowest risk ranges and a similar under-estimation in the highest ranges. Yet, these deviations are within 8% of perfect calibration, and all rates fall within the 95% confidence interval ranges.



4.3.3

Figure 4.3.3. Validation sample of children with febrile seizures: comparison of predicted recurrence probability and proportion of observed recurrences up to the age of 5 years in 5 quintiles of increasing risk. Number of episodes at risk per group and 95% confidence limits are shown.

Prediction of any recurrent seizure

Table 4.3.3 presents the estimated probabilities (with 95% confidence bounds) of febrile seizure recurrence within one year after the index seizure (Table 4.3.3a), and up to the age of 5 years (Table 4.3.3b) for children with different risk profiles. Probabilities are calculated for various age groups. There is a wide range in probabilities, from 0.06 for a 3 years old without risk factors to 0.93 for a child aged 12 months with 3 previous seizures, a positive family history and a temperature lower than 40.0° C at the initial febrile seizure. Highest probabilities are estimated for young children with a positive family history combined with a temperature below 40.0° C at the initial febrile seizure, and for children with previous recurrences. The confidence intervals around the probabilities are small.

Complex recurrences

A partial initial febrile seizure and a multiple initial febrile seizure (i.e., recurring within 24 hours) were retained in the final logistic regression model and considered risk factors for recurrences with complex features. A partial initial seizure was associated with an increased probability of complexity given a recurrence, while the presence of multiple initial seizures decreased this probability. Conditional probabilities of seizure complexity given a recurrence can be calculated from Table 4.3.4. Without risk factors, one in five recurrences has complex features. In case of a partial first febrile seizure the probability estimated from Table 4.3.3 should be multiplied by 0.44, and in case of a multiple initial seizure by 0.11.

In the validation study 13% of the children had at least one recurrence with a complex feature (Table 4.3.1). No details about the nature of the complexity were available (i.e., whether the seizure was partial, multiple, or of long duration), and we do not know if the complex recurrence was the first re-occurrence after the initial febrile seizure, or a later seizure. The predictive model for complex recurrences was not well calibrated, and showed a general under-estimation of probabilities.

Table 4.3.3a. Estimated probability of febrile seizure (FS) recurrence within one year after the most recent FS, by risk profile. Point estimates and 95% confidence intervals.

1st Degree family history	*Initial FS temp (°C)*	*Nr Previous seizures*	*Child's actual age (months)* 12	18
neg	≥ 40.0	1	.24 (.19–.29)	.15 (.12–.19)
pos	≥ 40.0	1	.34 (.30–.39)	.23 (.20–.26)
neg	< 40.0	1	.35 (.32–.38)	.23 (.21–.26)
pos	< 40.0	1	.49 (.46–.52)	.34 (.31–.36)
neg	≥ 40.0	2	.42 (.38–.46)	.28 (.25–.32)
pos	≥ 40.0	2	.57 (.54–.60)	.41 (.38–.43)
neg	< 40.0	2	.58 (.55–.60)	.41 (.39–.44)
pos	< 40.0	2	.74 (.72–.75)	.56 (.55–.58)
neg	≥ 40.0	3	.47 (.43–.52)	.33 (.30–.36)
pos	≥ 40.0	3	.63 (.60–.66)	.46 (.44–.49)
neg	< 40.0	3	.64 (.62–.67)	.47 (.45–.49)
pos	< 40.0	3	.80 (.79–.81)	.63 (.61–.64)

Example case

As an example, a child presenting after a second febrile seizure at the age of 15 month is discussed. The following risk factors are present: the first degree family history for febrile seizures is positive (its mother has suffered one febrile seizure as a child), the temperature at the initial febrile seizure exceeded 40.0° C, the child has experienced two previous febrile seizures. The first episode occurred at the age of 11.5 months. The probability of any recurrence within one year and at the age of 5 years can be estimated from Table 4.3.3, through interpolation. The recurrence probability over time up to the age of 5 years (and its 95% confidence bounds) is presented in Figure 4.3.4a. Up to the age of 36 months the probability increases steeply to about 60%, whereafter the increase is marginal. Figure 4.3.4b shows the probability of yet another (fourth) febrile seizure after the occurrence in this same child of a third episode at the age of 30 months. Since there are no risk factors for complex recurrences (i.e., a partial or multiple first episode), her risk of any complex recurrent febrile seizure is estimated to be about 10% (calculated from the recurrence probability at the age of 12 months, 0.21 times 0.50, Table 4.3.3b).

24	*30*	*36*	*42*
.11 (.01–.14)	.06 (.05–.09)	.04 (.03–.06)	.03 (.02–.05)
.16 (.14–.19)	.10 (.08–.12)	.06 (.04–.08)	.05 (.04–.07)
.17 (.15–.19)	.13 (.10–.15)	.10 (.08–.12)	.05 (.04–.07)
.25 (.23–.27)	.17 (.15–.19)	.09 (.08–.11)	.08 (.07–.10)
.21 (.18–.23)	.12 (.11–.15)	.08 (.06–.09)	.07 (.05–.08)
.30 (.28–.33)	.19 (.17–.21)	.12 (.10–.13)	.10 (.09–.12)
.31 (.29–.33)	.19 (.17–.21)	.12 (.10–.13)	.10 (.09–.12)
.44 (.42–.45)	.28 (.27–.30)	.18 (.16–.19)	.16 (.14–.17)
.24 (.21–.27)	.15 (.13–.17)	.09 (.07–.11)	.08 (.06–.09)
.35 (.32–.37)	.22 (.20–.24)	.14 (.12–.15)	.12 (.10–.13)
.35 (.34–.37)	.22 (.21–.24)	.14 (.13–.15)	.12 (.11–.14)
.49 (.48–.51)	.32 (.31–.34)	.21 (.19–.22)	.18 (.17–.20)

DISCUSSION

For many parents, it is extremely important that their child remains free of recurrent seizures during subsequent fever episodes. Alternatively, they may be more concerned about the long term consequences of antiepileptic drug treatment, particulary with regard to their child's cognitive development. [17] Obviously, individualized prognostic estimates of the risk of further seizures are basic to informed decisions regarding prophylactic measures.

As earlier studies have shown, febrile seizure recurrence rates show wide variation and depend on the presence of risk factors. [4–6] These studies have provided estimates of the average febrile seizure recurrence risk and have defined relative recurrence risks for certain risk factors. Such average risks and relative risks do not allow for accurate estimation in individual children with particular risk factors. The aim of the present analysis was to provide more accurate estimates of individual risk based on a joint set of clinical characteristics, and thereby to improve the discrimination between children who will and will not develop a recurrent febrile seizure.

Table 4.3.3b. Estimated probability of febrile seizure (FS) recurrence after the most recent FS up to the age of 5 years, by risk profile. Point estimates and 95% confidence intervals.

1st Degree family history	*Initial FS temp (°C)*	*Nr Previous seizures*	*Child's actual age (months)* 12	18
neg	≥ 40.0	1	.36 (.30–.42)	.24 (.20–.29)
pos	≥ 40.0	1	.50 (.45–.55)	.35 (.31–.40)
neg	< 40.0	1	.51 (.48–.55)	.36 (.33–.39)
pos	< 40.0	1	.67 (.65–.70)	.50 (.48–.53)
neg	≥ 40.0	2	.60 (.55–.64)	.43 (.39–.47)
pos	≥ 40.0	2	.76 (.73–.78)	.58 (.56–.61)
neg	< 40.0	2	.76 (.75–.78)	.59 (.57–.62)
pos	< 40.0	2	.89 (.89–.90)	.75 (.74–.77)
neg	≥ 40.0	3	.66 (.62–.70)	.49 (.45–.53)
pos	≥ 40.0	3	.81 (.79–.83)	.65 (.62–.67)
neg	< 40.0	3	.82 (.80–.84)	.66 (.64–.68)
pos	< 40.0	3	.93 (.92–.94)	.81 (.80–.82)

Based on a combination of independent risk factors, the presented model allows to estimate the probability of recurrences after an initial febrile seizure, and after a first and a second recurrence. The latter is particulary relevant from the clinician's point of view, since one is frequently confronted with a febrile seizure in young child that has already suffered previous febrile seizures. Especially after the first recurrence, fear may arise that the disorder will persist and will influence the child's further development, [18] and the paediatrician or paediatric neurologist is prompted to assess the further prognosis.

As our study shows, the probability of seizure recurrence after a febrile seizure depends on the child's attained age, the presence of risk factors (i.e., features of the first febrile seizure) and, in case of recurrences, the number of experience seizures. The most important factor is the child's age, with the highest recurrence probability between age 12 and 30 months. Risk factors consistently related to seizure recurrence are the presence of a first degree relative with febrile or unprovoked seizures and the child's temperature within one hour of the initial seizure. As recently shown in another study, a positive second or third degree family history is not associated with recurrences. [19] After the

24	*30*	*36*	*42*
.16 (.13–.21)	.11 (.08–.14)	.06 (.05–.09)	.05 (.03–.07)
.24 (.21–.28)	.17 (.14–.20)	.10 (.08–.12)	.07 (.06–.09)
.25 (.22–.28)	.20 (.18–.22)	.17 (.14–.19)	.07 (.06–.09)
.36 (.34–.39)	.22 (.20–.24)	.15 (.13–.17)	.11 (.10–.13)
.30 (.27–.34)	.21 (.18–.23)	.12 (.11–.15)	.09 (.08–.11)
.43 (.41–.46)	.30 (.28–.33)	.19 (.17–.21)	.14 (.12–.16)
.44 (.42–.46)	.31 (.29–.33)	.19 (.17–.21)	.14 (.13–.16)
.60 (.58–.61)	.44 (.42–.45)	.28 (.27–.30)	.22 (.20–.23)
.35 (.32–.38)	.24 (.21–.27)	.15 (.13–.17)	.11 (.09–.13)
.49 (.46–.52)	.35 (.32–.37)	.22 (.20–.24)	.17 (.15–.18)
.50 (.48–.52)	.35 (.33–.38)	.22 (.21–.24)	.17 (.15–.19)
.66 (.65–.67)	.49 (.48–.51)	.33 (.31–.34)	.25 (.24–.27)

occurrence of one or two recurrent febrile seizures, the hazard of further episodes is elevated 2 to 2.4 times. The high precision in the estimates in this study is a result from the fact that the estimates are based on the full dataset of 3,337 episodes at risk.

Still, other factors must play a role in precipitating recurrent febrile seizures, such as the child's susceptibility to infections, the number of febrile episodes and parental management of fever. So far, we have little insight into the clinical significance of these factors and whether they may be influenced by medical intervention. Future studies should focus on these factors.

The present findings with regard to the probability of recurrences with complex features are of considerable interest. In our previous report, [7] we found that subsequent complex seizures occur in 7% of cases, usually as multiple febrile seizures. Prolonged recurrences and recurrences with combinations of complex features occurred in only 2%. Using another analytical approach, risk factors found to relate to complex recurrences were an initial partial seizure, age less than 12 months at the first febrile seizure and a family history of unprovoked seizures. In the present analysis we found that a partial initial febrile seizure increased the probability of a complex recurrence and a

Table 4.3.4. Frequency of complex recurrences among children with at least one recurrence.

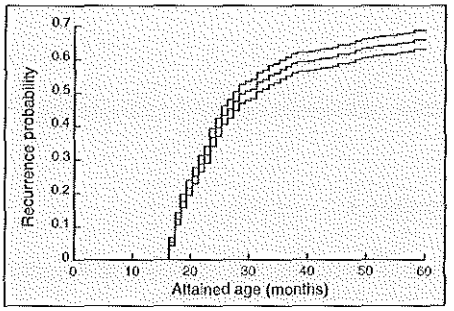
*Risk Factor**	*Complex recurrence n (%)*	*Simple recurrence n (%)*	*Total n*
Partial initial FS	8 (44)	10 (56)	18
Multiple initial FS	9 (11)	77 (89)	86
Both a partial and multiple initial FS	0 (0)	1 (100)	1
None of the two	105 (21)	392 (79)	497
Total	122 (20)	480 (80)	602

FS: febrile seizure
* Selected by logistic regression analysis, contrasting complex with simple recurrence.

multiple initial episode decreased the risk of a complex seizure *given* a recurrence. Moreover, these two factors were found to be mutually exclusive in children with recurrences (Table 4.3.4). There are at least three possible explanations for the latter finding.

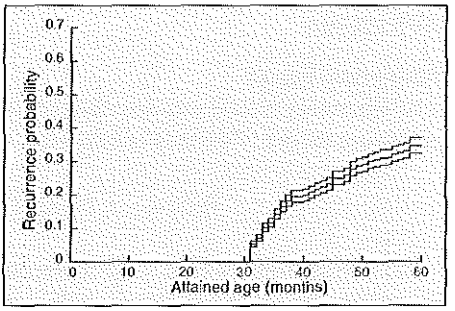
First, since the numbers were quite small, all this could be a chance event. Second, the coding of the type of initial seizure in the original studies could have been such that the presence of a partial seizure precluded the presence of another complex feature. This appeared not to be the case. Of all 2,496 first seizures, 11.4% were multiple (Table 4.3.1), including 19 children with multiple seizures in combination with partial features. On average, 2% of all first febrile seizures had combinations of complex features (Table 4.3.1). Since this finding cannot be explained based on the data structure, other explanations can be considered. Partial febrile seizures and multiple febrile seizures may be quite separate entities. We speculate that the fact that a child develops two or more generalized febrile seizures within 24 hours reflects a temporarily impact of a high temperature on a vulnerable brain, and is not necessarily be associated with further (complex) seizures. In contrast, partial febrile seizures exhibit focal cerebral frailty, predisposing the child to complex recurrences.

Unfortunately, the actual type of recurrence complexity, whether partial, prolonged or multiple, could not be studied, because this information was not consistently available in the data set. The fact that the fit of the predictive model for complex recurrences was poor, may be related to this lack of detail in the model. Also, we do not know if the complex recurrence was the first recurrence or a later seizure, occurring after several simple febrile seizures. Any meaningful relation with the number of experienced seizures during follow up can therefore not be conjectured. It is obvious that details on the nature of complex recurrence seizures and their timing would give more



4.3.4a

Figure 4.3.4a. Illustrative case: a 15 month old child with a second febrile seizure with a positive first degree family history of febrile seizures. Probability of any recurrence with time up to the age of 5 years. Estimate and 95% confidence limits are shown.



4.3.4b

Figure 4.3.4b. Case from Figure 4.3.4a. Probability of further recurrences with time up to the age of 5 years after a third febrile seizure at the age of 30 months. Estimate and 95% confidence limits are shown.

insight into the natural history of recurrent febrile seizures for a small, but important group of children. Future follow up studies should focus on this issue, which has direct implications for practice. Until the results of such studies are available, and our predictive model concerning complex recurrences can be re-validated, the predictions reported here should be used with great care. Yet, they are the only available at present.

CONCLUSIONS

The risk of recurrent seizures in a child with febrile seizures can be assessed by considering age, family seizure history, temperature at the initial seizure and a history of previous recurrences. These factors should be used in combination. Our risk functions yields accurate and precise risk estimations, which may be used as a tool in counselling and reassuring parents, and—with regard to additional prophylactic measures—indicate which children are most likely to benefit from treatment. The predictive model for complex recurrences needs further development before it can be used in practice.

APPENDIX

Recurrence hazard

The recurrence hazard was described as a function of calender age by the Cox multiple regression model, [15] defined as follows:

$$\lambda\,(t, x_1 \ldots x_n) = \lambda_0\,(t)\,\exp\,(b_1x_1 + \ldots + b_nx_n),$$

In this equation, $\lambda\,(t, x_1 \ldots x_n)$ represents the recurrence hazard, expressed as number of recurrences per unit of time 'at risk' at age t for a child with risk factors $x_1 \ldots x_n$. Risk factors are coded as 0 = absent and 1 = present; $b_1 \ldots b_n$ represent their regression coefficients estimated from the data. Here, t was taken as the calender age of the child, rather than the length of follow up. $\lambda_0\,(t)$, the recurrence hazard as a function of calender age for $x_1 \ldots x_n = 0$, was estimated according to the method of Kalbfleish and Prentice. [20] Thus, the risk model as defined above describes the recurrence hazard as a function of calender age and risk factors despite the fact that age is not represented in the model as a covariate. An example of an age-based hazard is given by Breslow and Day. [21] On the risk factor coding used, a positive regression coefficient b_n indicates that the hazard is higher in the presence of the risk factor concerned than in its absence. As the child's temperature at the first seizure was always missing in one study, [8] an indicator of missingness was introduced in the model for this variable. [20]

Recurrence risk in individual children

The probability of seizure recurrence before calendar age T_2 for a given child with a present age T_1 ($T_2 > T_1$) and risk factors $x_1 \ldots x_n$ was estimated as a step function according to Breslow: [22]

$$P(T_2|T_1, x_1 \ldots x_n) = 1 - \exp\{[-\exp(b_1x_1 + \ldots + b_nx_n)]\Lambda 0(t)\}.$$

where $P(T_2|T_1, x_1..x_n)$ represents the aforementioned probability and $\Lambda 0(t)$ represents the $\lambda 0(t)$ as defined above, integrated from T_1 to T_2. The 95% confidence interval of this probability is based both on the variance of $\Lambda 0(t)$ and the variance of $(b_1x_1 \ldots b_nx_n)$, and was calculated as described by Tsiatis. [22]

Risk of a recurrence with complex features

We used a logistic regression function that estimates the conditional probability of a complex recurrence *given* a recurrence and a set of risk factors. All potential risk factors known at the initial seizure were candidates to be removed from the full multivariate model if their regression coefficient met a significance level < 0.05. To derive the model the SAS procedure LOGIST was used (SAS Institute Inc., Carry, N.C.). For each combination of the risk factors thus identified, the conditional probability of a complex recurrence was calculated using the formula

$$P(CR, x_1 \ldots x_n) = P(R) \times P(ClR, x_1 \ldots x_n),$$

where $P(CR, x_1 \ldots x_n)$ is the probability of a complex recurrence given risk factors $x_1 \ldots x_n$, P(R) the probability of any recurrence, and $P(ClR, x_1 \ldots x_n)$ the conditional probability of complexity *given* a recurrence and the presence of the risk factors $x_1 \ldots x_n$.

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5
General discussion

In this chapter, information about a real patient is presented in stages (boldface type) to a paediatrician, who responds to the information and shares his reasoning with the reader (regular type). A commentary follows.

A CASE HISTORY

A 19 month old boy is rushed into the emergency department after being found unconscious at home by his mother. She was about to wake him from his afternoon nap when she heard a short cry from his bedroom. He was found lying on his back, rigid and unresponsive, apparently not breathing well, with blue lips. When she took him in her arms he grunted and shook. She immediately dialled the local emergency number and did not call the family's general practitioner. The boy was transported to hospital by ambulance. On arrival in the emergency room breathing and circulation are adequate. His pulse rate is 110 per minute, blood pressure 100/60 mm Hg, and temperature 39.9° C.

The first thing is to make sure if the child is stable. Is there a focus for the fever? Is he awake, are there neurological signs?

On examination, the boy is somnolent but he can be waken up. He appears confused but seems to recognize his mother. The Glasgow Coma Scale is M3 V2 E2. There is a mild generalized hypotonia. He is somewhat resistive. Breathing is adequate, there is no cyanosis. The circulation seems stable with a regular pulse and prompt capillary refill. Apart from a slightly red pharynx there is no obvious focus of infection. The skin is unremarkable. There are no enlarged lymph nodes. Nuchal rigidity and Kernig and Brudzinski signs are difficult to evaluate since he resists actively and refuses to sit.

The boy appears stable. A urine bag should be attached. Further information on the history would be useful: Have there been previous such attacks? Has he had frequent fevers? Any neuro-developmental abnormalities? Is there a family history of neurological disease, in particular febrile seizures or epilepsy?

The boy was born after an uncomplicated pregnancy and delivery. Growth and development have always been satisfactory. He has received his immunisations according to schedule. Apart from a fever up to 39.0° C during one day after the second and third immunisation, he has always been well. Both his mother and her elder brother suffered two or three short attacks with loss of conscience before the age of 4 years, but it is unclear if there were any precipitating factors at the time. At present they are in good health, no relatives are known to have epilepsy or febrile seizures.

Possibly there is a familial predisposition to seize under at least some circumstances. But then again these attacks may have been non-epileptic and have no relation with the present problem. The rest of this history is not very helpful. Can the mother give a more detailed description of the attack? How long did it last? Were there repetitive clonic movements? Was he well before the event?

Two days before the attack, he had a running nose and a temperature elevation to 37.9° C. His appetite was poor. The day before the episode, temperature was normal but he still was somewhat quiet and listless. In the morning he had taken two cups of tea with milk but he had refused his sandwich. He was tired and went to sleep an hour earlier than normal. About the attack itself, the mother admits she cannot remember everything as it was a frightening sight. The boy looked blue and twitched. There were shaking movements of the whole body. She thought he was dying. His eyes were turned upward, he didn't react to calling. The duration may have been 5 to 20 minutes. On arrival of the ambulance he was still unresponsive and faintly twitching. During the ride to the hospital he did not vomit or cough. There is no evidence of accidental ingestion of medications.

This history is suggestive of a convulsive event but it is atypical. We have been taught that a simple febrile seizure occurs in the beginning of a febrile illness, in particular when the temperature is rising. With his diminished food intake due to a lack of appetite, the attack may also be a manifestation of hypoglycaemia, or some other metabolic derangement, or a febrile seizure. Although maybe less likely, meningitis cannot be ruled out. Alternatively, it could be a case of gastro-oesophageal reflux with aspiration and cyanosis or a paroxysmal cardiac event. As an attending paediatrician, I want to admit him for observation and do a few laboratory tests. Given the fever, I would be interested in the results of a complete blood count, urine sediment, and serum glucose. Also, a lumbar puncture should be done, for it is well known that shortly after a seizure the signs of meningeal irritation may be absent in a child with meningitis.

The white cell count was 13,500 per cubic millimetre with a normal differential. Haemoglobin was 7.3 mmol/l. Urinalysis was unremarkable. The serum glucose was 4.9 mmol/l, sodium, potassium and calcium concentrations were normal. The lumbar puncture procedure was unsuccessful the first time, and when tried one level higher resulted in a 'traumatic tap' with 30,000 red cells and 240 white cells per cubic millimetre (20 percent lymphocytes, 80% segmented cells). The gram stain was negative.

All this does not seem to be contributory. Given these results I would not give antibiotics at this point but have the resident check him every hour for meningeal signs and skin lesions. If he doesn't improve within two to four hours, I would treat empirically with wide spectrum antibiotics.

Two hours later the boy sits up in his bed with his mother at his side. He drinks and plays a little. He is cooperative on examination, looks tired, his temperature is 40.2° C, respiratory rate 38 per minute. He can flex his neck without difficulty. The next day he is seen walking around the ward and riding a bicycle. The temperature is normal. After two days of observation he is discharged. The mother is told that her son has suffered a febrile seizure. The cause of the fever has probably been a viral infection. Three weeks after this episode, he is seen in the outpatient clinic at a regular follow up appointment. Since discharge from the hospital, he has been well. There has been no fever and no abnormalities in behaviour. The mother says that, in general, he seems even better than before. There has been a rapid increase in vocabulary. On examination the boy appears in perfect health, he is in good humour and plays with the doctor's stethoscope. His mother is calm now and says that she has been thinking things over. Her questions are: Can this happen again? What can be the consequences of a recurrent episode, and is there some way to prevent recurrences?

I am still not sure about the exact diagnosis. Given the present outcome, he seems to have suffered a first febrile seizure of uncertain duration. In combination with a possible positive first degree family history this suggest an increase in risk of recurrent seizures during future fever episodes, probably over 50%. However, I do not think that one can give a confident absolute recurrence risk in an individual case. I am not sure whether in children with a long lasting initial febrile seizure or with a positive family history such recurrences might be atypical and pose a potential danger to the brain. Maybe an electroencephalogram will be helpful. I can assure the mother that the mortality in children with febrile seizures is extremely low. And of course, I would like to safeguard the child and the family from the frightening experience of another seizure. At this point I decide to discuss the options of continuous treatment with phenobarbital, and of intermittent treatment with diazepam or a acetaminophen suppository during the next febrile episode. These measures have all been claimed to lower the recurrence risk and they may reduce parental anxiety. A strategy of watchful waiting is also justified. I believe that in this case there is no absolute truth about the best approach. In any event, I prescribe a dose of 5 mg rectal liquid diazepam to stop a seizure at home and, teach the mother how to administer it, and give her some general advice what to do in case of a new seizure.

The EEG performed one week later is normal, and at the following telephone call the mother indicates that she prefers expectant management over preventive medication. An appointment after 3 months is made.

COMMENTARY

From this case, many clinical and laboratory clues emerge of which the interpretation is difficult. Some of them have direct consequences for the management. As stated in Chapter 1, various outcomes after a seizure with fever are possible, ranging from the totally benign to persistent neurological impairment. The efficiency of the emergency room decision-making process, i.e., the directness of the route from initial patient contact to formulation of the most likely diagnosis and optimal management plan are evidently related to the knowledge and experience of the physician plus additional factors, customarily referred to as clinical judgement. The latter can be described as the physician's ability to use knowledge in its proper order and to balance the medical cost and benefits of alternative management strategies. This implies dealing with diagnostic and prognostic uncertainty. In this section we will examine the clinician's questions, and review the findings of the studies described in this thesis in as much relevant to management.

After presentation to the emergency room, the physician will, as in any acutely ill patient, check the child's vital functions and signs of ongoing seizure activity. Due to inadequate breathing during an ongoing seizure, hypoxia may be present and supplettion of oxygen is indicated. Also, in the postictal state following a seizure breathing can be insufficient. Modern treatment of ongoing seizures can be found in textbooks, and in the report of a recent National Institutes of Health consensus conference. [1]

The history of the event is crucial, but often difficult to obtain in detail. A seizure can occur with such a rapidity that it is impossible for an observant adult to witness the entire episode. As partial observers, the parents may not be able to reconstruct the course of events with enough accuracy to make the history complete. Further, most unprepared parents interpret a seizure as a near death event, and they are often so overwhelmed that they cannot reproduce what has exactly happened. [2,3] Of special interest is the presence of complex seizure features (i.e., focal, prolonged, or multiple). Berg et al. recently found that a careful interview, on average 23 days after a seizure, resulted in a substantially higher yield of complex features, as compared to emergency room records. [4] In another study, based on a second interview with the witness and the emergency room chart, three paediatric neurologists agreed in the rating of multiple and prolonged features. [5] There was disagreement about focal features in 23 out of 100 seizures. [5] These results suggest that complex features may be under-reported or unrecognized during the emergency room evaluation. Unfortunately, there is no way around the inherent un-reliability of the clinical history. Neither elevated serum creatinine phosphokinase at the time of the emergency room evaluation, [6] nor an abnormal acute electroencefalologram will prove that a seizure occurred. [7] Hippocrates is still right, it is only the history that counts (Chapter 1).

The notion that 'classical' febrile seizures occur mostly during a rapid increase in temperature is deeply entrenched in the teaching of paediatrics. As Berg recently observed, there is no evidence for this hypothesis since this has never been studied. [8] There is, however, evidence that the height of the temperature during a febrile illness is

associated with the likelihood of a seizure, and that each child has his or her own threshold above which a seizure may occur. [8–10] From the clinician's point of view, all this is irrelevant, as the temperature just before and during an attack in an individual case is almost never known. Anyhow, the clinician will frequently encounter children with febrile seizures that have a history of fever during the days prior to the attack. Nevertheless, in considering the differential diagnosis at presentation the duration of fever is important, since a longer existing illness appears to be associated with an increased probability of meningitis (Chapter 3).

Routine acquisition of laboratory investigations regardless of clinical features including chemistries, toxic screen, cultures, radiography and CT has a low yield. [11–13] Therefore, any attempt to confirm a specific etiology for the seizure by further diagnostic investigation and/or laboratory tests should be guided by the history and physical examination.

THE POSSIBILITY OF MENINGITIS

Hippocrates not only recognized that seizures occur in children under different circumstances, he also observed that most are benign. Nevertheless, meningitis may present as a seizure associated with fever. The question is whether a seizure can be the sole manifestation of meningitis in an otherwise well-appearing child. One would expect that in such cases the child is in an advanced stage of a potentially debilitating disease. According to Stephenson, [14] seizures in paediatric meningitis and encephalitis can be categorized in—

- prolonged hemiclonic seizures (as seen in herpes simplex virus 1 encephalitis), suggesting secondary focal pathology;
- tonic seizures with impaired ability to localize pain, which suggests ischaemic mechanisms with brain swelling;
- movement disorders such as chorea;
- generalized short seizures, as in seizures with fever but without meningitis.

It is the presence of simple seizures that has fuelled the discussion about the need for routine lumbar punctures in children with seizures in association with fever.

Several authors have recognized that young children with meningitis may lack meningeal signs and recommend routine lumbar puncture in all children with seizures and fever. [15–17] However, others have suggested that in most such cases there will be other symptoms and findings that point to meningitis. The uncertainty surrounding this issue has led to a legitimate difference of opinion about the best way to approach young children with seizures and fever.

RATIONAL ACUTE MANAGEMENT

The decision to perform a lumbar puncture (LP) in an individual child is influenced by many factors. One is the perceived *probability of meningitis.* Other factors are the *hazards and drawbacks* of routine LP, the potential *dangers of a delayed diagnosis* of meningitis, the *sensitivity and specificity* of the LP itself, and the *reliability of the history and physical findings.*

As discussed in Chapter 3, the prevalence of meningitis among children with seizures and fever in paediatric emergency wards is between 1% and 3%, and depends on the clinical presentation.

With few exceptions, a LP must be performed whenever the diagnosis of meningitis is suspected to confirm the diagnosis and determine the antibiotic sensitivity of the bacteria. Exceptions occur with raised intracranial pressure or severe illness such that meningitis can be diagnosed clinically and bacteria isolated from the blood culture. [18,19] In these cases, intravenous antibiotics should be given immediately after blood is drawn for culture. Further reasons to avoid LP are known coagulation disorders or skin infection at the puncture site. When the risk of meningitis seems low, but there may be bacteraemia, is it possible that a traumatic LP might introduce bacteria to the central nervous system. [20,21] Although experimental work on bacteraemic dogs has made this sequence plausible, in humans it has been difficult to prove. [22] Other complications of LP include the creation of epidermoid cysts, particulary after multiple non-successful LPs. [23,24] Finally, undergoing a LP is a traumatic experience for any toddler, and the need to carefully discuss the reasons for the LP with the parents takes time and attention. [25]

Bacterial meningitis requires immediate antimicrobial treatment. Although almost every clinician knows of meningitis cases with late treatment due to parental or doctor's delay, it is unclear to what extend this influences the efficacy of antimicrobial treatment. [26] This reflects a basic problem in the study and management of seizures and meningitis: at which point in the course of the disease will the patient come to the attention of a physician, and will a seizure be an early or a late manifestation?

Several investigators have pointed to the low sensitivity of LP in the early stages of meningitis and the risk of relying on an initially reassuring test result. [27–31] Conversely, there are reports of pleocytosis after seizures or head trauma, in the absence of infection. [32] There are other situations when the LP result is unreliable. [33,34] Thus, both false negative and false positive LP results may mislead the clinician. False negatives are likely to be the most dangerous, as they imply a failure to prompt treatment.

Several clinical signs and symptoms have been found to discriminate between children with and without meningitis. [35–38] Clinical 'risk factors' as postulated in an early study by Joffe et al. were confirmed in our two studies described in Chapter 3. [36] These factors were: physician visit within 48 hours before the seizure; occurrence of seizure(s) at the emergency room; focal, prolonged or multiple seizures; suspicious findings on physical examination (i.e., petechiae and signs of circulatory failure, or so called *Minor* signs); and abnormal neurological findings on physical examination (i.e., signs of

Table 5.1. Emergency room approach to the child presenting with a seizure associated with fever.

I	Check vital functions and seizure activity. *In case of ongoing seizure activity: oxygen and i.v. medication to terminate;* *appropriate treatment of obvious sepsis or meningitis cases.*
II	Perform physical examination and take history. *Coma?* *Other 'Major' meningitis features?* *Vomit at home?* *Complex seizure features?*
III	Assess meningitis probability in stepwise fashion.
IV	Weigh inconvenience and risk of LP procedure' and false negative rate of LP test results' against probability of meningitis; decide LP or expectant observation.
V	Treat underlying infectious disease, counsel parents, and arrange follow up.

LP = Lumbar puncture
' not studied in this thesis

meningeal irritation and various degrees of coma, so called *Major* signs). The child's age, gender, and degree of fever did not have any diagnostic value. When a child presents without these risk factors, the probability of meningitis is low. In fact, in the absence of meningeal irritation, petechiae or complex features of the seizure, there were no meningitis cases in either of our two studies.

These results indicate that it is indeed very unusual for a child with meningitis to present only with a seizure. Rather, seizures due to meningitis occur in clinically very ill children. As shown in Chapter 3, a fair number of children *without* meningitis will present with the risk factors mentioned above, i.e., the specificity of these 'clinical tests' is far from 100%. We assessed how many LPs would be performed if a sequential algorithm based on clinical risk factors was used. Using various stepwise inclusion rules of children with positive risk factors, the proportion of children with meningitis could be reduced to 0%, while saving 26% to 54% the trauma of a LP (Figure 3.1.2 and Table 3.2.4). Whichever category of clinical information is used first (i.e., the type of seizure, recent history or physical examination), all ended by identifying all meningitis cases at a somewhat varying 'cost' of (a posteriori) unnecessary LPs.

In this respect, other outcomes associated with the decision to either perform routine LPs in all children or perform LP only on clinical indication are relevant as well. In the decision analysis presented in Section 3.2 the possibility of a (post hoc) unnecessary hospital admission and intravenous antimicrobial treatment after a false positive LP

result is contrasted with a treatment delay of two to four hours in an initially missed case of meningitis. From the analysis it followed that only if delayed meningitis treatment leads to a substantial increase in meningitis mortality and morbidity as compared to early treatment, a routine LP approach yields an on average more favourable result. Yet, this is achieved at the cost of several hundreds extra LPs in children without meningitis per 1,000 children with a seizure with fever. On the other hand, if the LP procedure is associated with fatal and non-fatal complications, however low in frequency, performing routine LPs will always lead to excess mortality and morbidity. Unfortunately, no published studies exist that give insight in the risk of such complications.

In conclusion, the probability of meningitis in infants and children with seizures and fever is low. The clinical manifestations of the disease are not limited to signs of meningeal irritation. A longer existing febrile illness, vomiting and drowsiness are well known symptoms that will be disturbing to the experienced clinician. Conversely, meningitis is highly improbable in a child without the risk factors described. We believe that there is no need for routine investigation of cerebrospinal fluid, provided that careful follow up is available. The typical child with a febrile seizure (i.e., without meningitis) usually recovers within one hour after the attack, showing no clinical signs of severe illness thereafter.

Given the history and the physical examination, the boy presented in the case should have been considered at a low risk of meningitis, and an expectant observation (without LP) would have been justified. In each individual case of a child that presents in the emergency room with a seizure associated with fever, the clinician has to decide what the optimal approach is. A guideline is summarized in Table 5.1.

HOSPITALISATION

Hospital admission after a seizure associated with fever is often not necessary. It should be reserved for children for whom additional investigations are necessary or who have a febrile disease that should be treated in hospital. One could argue that in the presented case hospitalization for two days might have led to nosocomial infection, a risk that this child would infect other children, a negative psychologic impact on the child, and financial cost. Short term observation in an outpatient facility is to be preferred. As stated before, the child with a febrile seizure will usually recover within one or two hours. Occasionally, hospitalisation is necessary for alleviating parental anxiety. Although in childhood the degree of fever may not reflect the severity of illness, parents become distraught and reassurance is difficult when the cause of fever cannot be identified.

THE GENERAL PRACTITIONER

In this case, the general practitioner (GP) was not called. As shown in Chapter 2, in the Netherlands probably up to 50% of all episodes of a seizure associated with fever are

managed at home by the GP. We do not know whether cases of meningitis or other underlying diseases are diagnosed with a delay. From the questionnaire study described in Section 2.2 we get the impression that GPs will refer all children that suffer 'atypical' (i.e., complex) seizures to hospital. Valid advice on how to diagnose children with meningitis at home can be derived from this thesis. Whether it is necessary to validate this advice in a study directed specifically to the general population is another matter.

SEIZURE RECURRENCE

The main 'sequela' of a febrile seizure is a recurrent seizure during a subsequent febrile illness. [39] Knowing that a simple febrile seizure does no harm, the clinician and parents will be especially interested in the risk of frequent or severe recurrences that might, conceivably, carry some risk of persistent neurological damage. In children considered at an increased risk, prophylactic treatment might be started, while the risk of just one or two uncomplicated recurrent seizures would probably not justify such treatment. Based also on the findings described in Chapter 4, the most important risk factors are age, a first degree family history of seizures, and the temperature at the initial febrile seizure (see Table 4.2.3).

The most important factor is the child's *age*. The highest recurrence hazard is present between age 12 and 30 months (Figure 4.2.3). Obviously, during this period the central nervous system is evolving, and at one period in its development it is apparently prone to seizures when there is fever, and subsequently becomes resistant to the impact of fevers. Given this conjectured underlying process of brain maturation, the influence of all other risk factors should be viewed against the background of the child's age.

Another factor consistently related to seizure recurrence is the presence of a *first degree relative with febrile or unprovoked seizures* (Table 4.2.2). A positive second or third degree family history is not associated with recurrences. [40] Family history is not related with the age at febrile seizure onset nor with the presence of other risk factors, and retains its predictive value for further seizures even after one or two recurrent seizures (Table 4.2.2).

The child's *temperature* within one hour of the initial seizure is also predictive of recurrence (Table 4.2.2). The higher the temperature, the lower the recurrence risk, a finding that fits the threshold concept described by Aicardi. [10] Nevertheless, the temperature measured at any time after the seizure may be a poor reflection of the actual temperature at the time of the seizure. Usually, when a child suffers a seizure the temperature will not be measured immediately. Thus, the significance of the temperature will remain subject to uncertainty. Unless the parents have indeed obtained a reliable measurement, temperatures measured longer than an hour after the seizure or historical temperature values should be rejected as invalid for recurrence risk assessment.

Complex features of the first seizure have long been thought to predict recurrence. The follow up studies described in Chapter 4 have shown that only multiple initial seizures are associated with a slight increase in risk for a first recurrence (Table 4.2.2). As no relation between the height of the temperature at the seizure and a multiple first

seizure was found, these children obviously have a lowered threshold to seizures, and may thus be at a somewhat increased risk of recurrence, at least for some period of time. Prolonged or focal initial seizures do not seem to be associated with this increased risk, as long as they have not led to permanent neurological abnormalities. Yet, given a recurrent seizure, the fact that the initial seizure was focal raises the probability of complexity for that recurrence (Section 4.3). Thus, the old concept of 'a complex initial seizure'—suggesting increased recurrence risk—should be abandoned, and the individual component features should be considered alone.

After a recurrent seizure, the same risk factors (except multiple seizures) retain their ability to predict further recurrences. But, in association with the child's attained age, a *history of previous recurrent febrile seizures* per se, turns out to be the strongest predictor of further seizures Table 4.2.3). As demonstrated in Section 4.2, the recurrence hazard after a second or third episode was highest between the ages of 12 and 36 months; thereafter, the recurrence hazard decreased to practically zero by age 5 years. Thus, there appears to be a critical age period for seizure recurrence, both for a first and for further recurrences. In addition, the length of the time since the initial (or previous) seizure holds further predictive information (Section 4.2). During the first 6 months after a febrile seizure, risk of recurrence for otherwise similar children is increased with a factor 1.7, as compared to the period thereafter (Table 4.2.3).

Information about complex and prolonged seizures after an initial simple or complex febrile seizure is relatively scarce. The collaborative study described in Section 4.2 found complex recurrences in 7% of all children with a first febrile seizure—mainly multiple seizures. Prolonged recurrences or recurrences with combinations of complex features occurred in 2%. Risk factors for such complex recurrences were an initial focal seizure, age < 12 months at the first febrile seizure and a family history of unprovoked seizures (Table 4.2.4). The latter two factors were associated with recurrence per se, and the analysis of risk factors for complex seizures *given* a recurrence (Section 4.3) identified only partial initial seizures to be associated with subsequent seizure complexity. Thus, in the described case, the risk of a complex febrile seizure is estimated to be between 7% and 10% (see Tables 4.3.3 and 4.3.4).

ELECTROENCEPHALOGRAM (EEG)

In the presented case, an EEG was performed. Although not examined in this thesis, a few remarks on the utility of an EEG are in order. Since the National Institutes of Health consensus in 1980, when the role of the EEG was said to 'remain controversial', [41] most authors have stated that routine EEGs do not add to the management of children with seizures and fever. [7,42,43] Stores concludes that early postictal EEGs are not useful to differentiate other attacks from actual seizures, will not identify cerebral infective actiologies and do not distinguish between simple and complex seizures. [7] Furthermore, the predictive value for the recurrence of either febrile or nonfebrile seizures is practically zero. [7]

Table 5.2. Prediction of febrile seizure (FS) recurrence: present status of risk factors.

	Status	*Source*
I. Determinants of recurrent seizures present at first FS		
neurodevelopmental problems	established	[63]
first degree family history of FS or epilepsy	established	TT
second degree or other family history of FS or epilepsy	not likely	[40]
gender	not likely	TT
first FS episode characteristics:		
age at onset	established	TT
temperature at time of first FS	established	TT
duration of fever before first FS	possible	[65]
multiple first FS	possible	TT
partial features	unlikely*†	TT
long duration	unlikely*	TT
neurodevelopmental damage after first FS	likely	NDA
type of infection at first FS	possible	NDA
II. Recurrence risk modifiers after the initial seizure		
age at subsequent fever episodes	established	TT
number of fever episodes	established	[66]
infection susceptibility or immunologic suboptimality	possible	NDA
febrile response to infections	possible	NDA
type of infection	possible	NDA
use of antipyretics	possible	[62]
use of other cooling methods	possible	NDA
continuous antiepileptic prophylaxis	possible	[54]
intermittent antiepileptic prophylaxis	possible	[56]
III. In case of seizure recurrence		
number of recurrent seizures	established	TT
age at recurrent seizure	established	TT
temperature at recurrent seizure	possible	NDA
type of recurrent seizure	possible	NDA
acquired neurodevelopmental damage	likely	NDA

* Provided no neurodevelopmental damage occurs.
† Possibly associated with occurrence of a complex seizure.
[.] Reference number.
TT This thesis.
NDA No data available.

Still, EEGs are widely used. In a 1989 survey of 500 practitioners that care for children in Illinois, Millichap found that 52% of the respondents would use the EEG in determining the need for phenobarbital prophylaxis. [44] Abnormalities such as spikes, sharp waves or spike-wave complexes can be seen in 15% to 55%, while slow waves are found in the early days following a febrile seizure in up to 88%. [7] In earlier studies, paroxysmal EEG abnormalities were found more frequently in children aged 3 to 6 years, in those with focal and prolonged febrile seizures and after a number of previous seizures. [45] This was again demonstrated in a recent population based study where spikes, sharp waves and spike-wave complexes were seen in 22% of a series of 676 children with febrile seizures. [56] Focality and longer duration (>15 minutes) of the initial febrile seizure, and the number of previous febrile seizures were associated with EEG abnormalities. Older age (>3 years) was associated with EEG abnormalities, irrespective of the number of seizures. This indicates that age may be the main determinant of EEG abnormalities. These studies failed to show that any of the EEG abnormalities predicted recurrent febrile or nonfebrile seizures. Thus, in the older child with a first seizure with fever (or a first recurrence), the chance of finding EEG abnormalities is substantial and caution in drawing conclusions remains warranted.

One other EEG study should be noted. Doose and Baier found that 4 to 7 Hz theta activity (theta rhythms) in children with febrile seizures was followed by spike and wave discharge on subsequent EEGs in up to 63% of cases. [47] In earlier studies these investigators found a relation between rhythmic theta and seizure recurrence. To date, these observations have not been confirmed. To increase our understanding of the mechanisms that produce recurrent febrile seizures, future studies might focus on the presence of paroxysmal EEG activity or theta rhythms in children during episodes of fever.

Thus, until their diagnostic and prognostic value is established, the use of routine EEGs is not recommended.

FEBRILE SEIZURE RECURRENCE RISK

In summary, the risk of recurrence in a child with a febrile seizure can be assessed by considering age, family seizure history, temperature at the initial seizure, time since the previous seizure and a history of previous recurrences (Table 5.2). The EEG is not helpful. As discussed in Section 4.2, other factors must play a role in precipitating recurrent febrile seizures, such as the child's susceptibility to infections, the number of febrile episodes and parental management of fever (Table 5.2, part II). So far, we have little insight into the clinical significance of these factors and whether they may be influenced by medical intervention.

PROPHYLACTIC TREATMENT

Surveys on febrile seizure management indicate that up to 90% of all clinicians use continuous antiepileptic prophylaxis (AEP) with phenobarbital or valproate to prevent recurrences in children considered at increased risk for recurrence. [48–50] The decision to

treat after a first seizure should rest on a comparison of medical cost and benefits. Several authors have questioned the use of daily AEP after febrile seizures. [51–53] Considering the benign nature of the disorder, the disappointing results of AEP trials to reduce recurrences and the frequent behaviourial and cognitive side effects of the antiepileptic drugs used, the experts' conclusion in these articles is that children with febrile seizures should not be treated with phenobarbital or valproate. Others maintain that phenobarbital is the safest drug available for prevention of recurrences and have advocated its use in selected children for a limited time, e.g., 12 months. [50,54] These authors suggest that children should be selected for treatment on the basis of risk factors or if they suffer recurrent seizures. From the recent literature, however, there is no consensus on whom to treat and for how long.

The data to back up these decisions are weak for several reasons. First, studies have focused mainly on a first recurrence and not on complex or protracted recurrences. Second, the efficacy of various drugs has been studied mostly by considering the overall recurrence rate in unselected children with a first febrile seizure. Some authors have defined 'high risk' groups for inclusion in their trials, but the 'high risk' criteria vary between studies. There are no reports on the efficacy of continuous AEP in subgroups of children with one, two, or more risk factors. Finally, no data are available on the influence of treatment on frequent recurrences. Given current clinical practice, medical knowledge is unlikely to increase in most of these areas; no large new clinical trials are expected. The decision to start AEP will therefore remain subject to considerable uncertainty.

CURRENT EXPECTATIONS OF CONTINUOUS ANTIEPILEPTIC PROPHYLAXIS

To assess the expected benefit and cost of continuous AEP, consider the following: If we assume that AEP would reduce the probability of a recurrence within a year by 30%, the boy in the case history (who has an estimated recurrence risk between 34% and 49%, see Table 4.3.3) would receive treatment for one year and still have a risk of a recurrent febrile seizures between 24% and 34%. This risk reduction of 10% to 15% means that it would take a one year's treatment of, on average, seven to ten identical boys to prevent one recurrence. The assumed relative recurrence risk under treatment of 0.7 is quite optimistic, and has not been substantiated by recent clinical trials. [51,52] The probability of behaviourial and gastro-intestinal side effects would be about 30%. [55]

Given the decline in recurrence hazard over time (Figures 4.2.3 and 4.3.1), the expected gain in prevented recurrent seizures is only marginal after 6 months of successful treatment. Therefore, daily prophylactic treatment (if any) should be given for a short term and only during a child's period of highest risk of recurrence. This means that only young children with multiple risk factors would potentially benefit from AEP, starting after a first or second recurrence (Table 4.3.3). When informed about all these trade-offs, many parents are able to choose for or against continuous prophylactic treatment.

INTERMITTENT PROPHYLAXIS

To avoid the side effects of continuous antiepileptic drugs, rapid-acting anticonvulsants given only during fever periods have been used in an attempt to reduce the risk of recurrent febrile seizures. Phenobarbital at times of fever has been proven ineffective, probably because of the delay in achieving appropriate serum and tissue levels. [50] Thus far, only prophylactic diazepam, given orally or rectally, has been studied in placebo controlled trials. [56–59] Although an early trial has shown a reduction of 30% to 50% of recurrences, [56] more recent studies showed no benefit. [57–59] However, side effects such as irritability, hyperactivity, ataxia and somnolence are seen in up to 40% of treated children. [58,59] Hence, the evidence about the utility of intermittent benzodiazepines with regard to prevention of recurrences is at present conflicting, and more studies are under way.

Still, there may be other options. Probably the most common medical treatment in children with febrile seizures is the use of antipyretic drugs such as acetaminophen and ibuprofen as soon as fever is detected. [60] Since fever is essential for the occurrence of a febrile seizure, physicians and parents have deducted that antipyretics might prevent recurrences. Yet, surprisingly few studies have actually evaluated if such antipyresis leads to a reduction of recurrent seizures. The recurrence rate in the first year after a first simple febrile seizure was 25% in a group of children receiving antipyretic instruction in an early study, not lower than the rate expected. [61] As shown in a recent Finnish trial, oral acetaminophen prescribed during subsequent illness did not reduce the number of recurrences as compared to placebo. [59] In an editorial commentary, it was concluded that acetaminophen may be useful in making a febrile child feel more comfortable, but so far this is its only benefit in relation to febrile seizures. [60]

The utility of an oral solution of ibuprofen during fever episodes is currently examined in a placebo controlled trial among children considered at increased recurrence risk in the Netherlands. [62] Until the results of this study and other current studies in the field are available and show a significant reduction in recurrence risk, the parents must be counselled that intermittent medication will not prevent recurrent febrile seizures.

RATIONAL MANAGEMENT OF RECURRENT FEBRILE SEIZURES

The mother in the case history asks if her child will suffer subsequent seizures and if there is some way to prevent such recurrences. The answers to these questions are basic to competent and effective medical care in this case. Our clinician doubts if '... one can give a confident absolute recurrence risk in an individual case', and feels that '... in this case there is no absolute truth about the best approach'. Clearly, these concerns relate to the continuing uncertainty regarding the relation of the risk factors with the probability of recurrent febrile seizures.

The results presented in Chapter 4 allow for an improved discrimination between children who will and will not develop a recurrent febrile seizure. Fortunately, for most

children prophylactic medical treatment is not necessary from a health hazard point of view; the risk of debilitating sequelae is extremely small. [63] However, since seizures are a most unpleasant experience for both the child and the parents, in some cases prophylaxis may be advisable. Based on the findings and considerations presented in this thesis we formulate the following guidelines:

For a given child, the probability of frequent or potentially threatening recurrences can be estimated using the predictions described in Section 4.3 (see Table 4.3.3). If this probability is considered high enough to outweigh the disadvantages of prophylactic treatment, the child can be treated with a daily anticonvulsant, such as phenobarbital or sodium valproate. Alternatively, an intermittent strategy with diazepam or an antipyretic agent during fever can be organized. As the probability of seizure recurrence declines rapidly after six months from the previous seizure (see Figures 4.2.1 and 4.2.2, Table 4.2.3), any prophylactic treatment should be restricted in duration to six months. Only for children younger than 15 months departure from this rule seems justified (Figure 4.3.1).

Instructions on how to prevent complications of recurrent seizures should be given for all children. The parents should be taught to position the child for optimal airway patency, which is especially important in the event the child vomits. A prescription for rectal diazepam should be given, and the parents be instructed how to administer it. [64] After each episode of a seizure, the child should be evaluated by a physician.

Thus, the clinician's main role is to explain, and organize a scenario for the next fever episode. The parents need to be counselled, preferably during a follow up visit after the initial seizure. Through education, they can usually be helped to overcome the fears and anxiety that these seizures provoke. They need to understand the data—that febrile seizures do not lead to death, epilepsy, mental retardation, or cerebral palsy. When educated about the natural history of febrile seizures and their consequences, most parents will be able to participate in the decision making process regarding the prophylaxis of adverse outcomes. They will team up with their doctor to assure the optimal surveillance of their child after a febrile seizure.

CONCLUSIONS

1 Seizures occurring in association with fever affect four percent of all children in the Netherlands.

2 In the Netherlands, 50% of children with seizures and fever is treated at home by the general practitioner. Those with seizures of long duration or a recurrent episode are referred to hospital. In addition, about 40% of children seen in the hospital emergency room are self referred cases.

3 Seizures with fever have various causes, the more important one being bacterial meningitis. The prevalence of bacterial meningitis among children presenting in the emergency room with seizures and fever is between 1% and 3%.

4 The likelihood of meningitis in children with seizures and fever seen in the emergency room is high in the presence of petechiae, coma, nuchal rigidity and complex features of the seizure (i.e., multiple, partial, or with a duration longer than 15 minutes). In the absence of these signs and symptoms meningitis is highly improbable.

5 The probability of febrile seizure recurrence in subsequent fever episodes is related to the child's age, and is highest between 1 and 3 years. Six months after any previous seizure the probability of recurrent seizures declines rapidly. A positive first degree family history of febrile or unprovoked seizures, and a temperature below 40.0° C at the initial febrile seizure increase the probability of recurrent febrile seizures. After febrile seizure recurrence, the number of experienced seizures (whether 2, 3, or more) increases the probability of yet further seizure episodes.

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6
Summary

SEIZURES OCCURRING IN ASSOCIATION WITH FEVER ARE THE MOST COMMON NEUrologic disorder in paediatrics, and affect 2 to 4 percent of all children in Great Britain and the United States. So far, no Dutch data on their frequency are available. Despite the frequent nature of these seizures, debate continues regarding their management.

In the acute situation, the physician must judge whether there is an underlying illness that requires immediate, specific treatment. The most urgent diagnostic decision is whether to do a lumbar puncture. Here, the question is whether one can safely rely on the absence of clinical signs of meningitis. Lumbar puncture is not totally devoid of risk, and undergoing the procedure is a traumatic experience for any toddler. Therefore, in each individual case the physician will weigh the risk of meningitis against the inconvenience and risk of the lumbar puncture.

After resolution of the acute episode, the possibility of recurrent seizures during subsequent febrile illnesses will have to be addressed. In children considered at increased risk of frequent or complicated seizures, prophylactic medication might be prescribed. On the other hand, the risk of just one or two uncomplicated recurrent febrile seizures would probably not justify such treatment, which may be associated with adverse effects on the child's behaviour and cognitive development. Thus, the decision to treat rests on the risk-benefits ratio.

All these management decisions have to be made under conditions of diagnostic and prognostic uncertainty. At present, the data to back up these decisions are fragmentary.

In this thesis various sources of uncertainty surrounding the management of children with seizures associated with fever are investigated. The focus is on the diagnostic value of signs and symptoms of meningitis, and on the prognostic value of risk factors for subsequent seizures during new febrile episodes.

INTRODUCTION

In the Introduction (*Chapter 1*), the phenomenology of seizures with fever and the importance of the history for the differential diagnosis is discussed.

EPIDEMIOLOGY

As stated, there are no studies on the frequency of seizures with fever in the Netherlands. The epidemiology of this disorder in Dutch children is addressed in *Chapter 2*. The prevalence of seizures with fever and the steps that are taken before a child is seen at the emergency room of a hospital are investigated. The organization of the Dutch health care system, which leads to selection of children for hospital referral is highlighted.

In the study described in *Section 2.1*, the number of children with a history of febrile seizures was determined in 3570 children attending primary schools in the suburban area of the city of Rotterdam. At the age of six years, 140 had experienced at least one febrile seizure (3.9%, 95% confidence interval 3.3% to 4.5%). Of these, 14% had

experienced a recurrent seizure during the same febrile illness. Recurrent seizures in subsequent fever episodes occurred in 26%. The median age at onset was 18 months. One third of the children had visited the hospital directly after the seizure, and 6% had used anticonvulsant drugs for at least 6 months. Of all children, 5.4% had a positive first degree family history of febrile seizures. Children with a positive family history were at a 4.5-fold increased risk of experiencing febrile seizures as compared to children without a positive family history. The prevalence found in Dutch schoolchildren is comparable with the prevalence found in the United States and Great Britain.

Not all children with seizures and fever are seen in hospital. Using the data of two Dutch studies on seizures associated with fever in general practice, the proportion of children with a first seizure with fever that is *not* seen in emergency rooms is estimated. The results show that general practitioners manage around 50% of all episodes at home. Thus, a notable quantitative selection occurs in the Dutch health care system. Also, there is 'qualitative' selection, as most general practitioners indicate that they will only refer 'atypical' cases.

ACUTE MANAGEMENT

Questions regarding optimal emergency room management are addressed in *Chapter 3*. First, signs and symptoms that relate to the presence of meningitis in children with seizures and fever are identified in a case-referent study (*Section 3.1*). In a prospective study (*Section 3.2*) the results of this study are evaluated and extended. Using decision analysis, the yield of routine investigation of cerebrospinal fluid in all children was compared with a strategy of testing only on clinical indication (i.e., in the presence of suspicious signs and symptoms).

In *Section 3.1* the extent to which children with meningitis can be recognized on the basis of readily available clinical information among children with seizures associated with fever is assessed in 309 children consecutively seen with a first seizure associated with fever in the emergency room of two major children hospitals in the western part of the Netherlands. Among these, 23 (7%) cases of meningitis were diagnosed. These were compared with a reference group of 69 children with seizures associated with fever, but without meningitis, selected at random from the remaining 286 children. Four signs from the physical and neurological examination in the emergency room discriminated between children with and without meningitis: The presence of *petechiae*, definite or dubious *nuchal rigidity, coma or persisting drowsiness* and *paresis or paralysis* identified 21 of the 23 meningitis cases. Two children with meningitis but without any of these signs presented with *complex seizure features* (partial, multiple, prolonged). In the absence of such complex seizures or suspicious features in the actual febrile illness (*illness for at least 3 days, vomiting or drowsiness at home, a physicians visit in the previous 48 hours*), there were no meningitis cases. The results of this study indicate that meningitis in children presenting with seizures associated with fever can be ruled out on the basis of readily available clinical information, and that there seems to be no need for routine investigation of cerebrospinal fluid.

In *Section 3.2* a prospective study to evaluate the value of the signs and symptoms identified in *Section 3.1* in diagnosing meningitis is reported. Detailed clinical data were collected on 365 consecutive children with seizures and fever at presentation, and *before* results of the cerebrospinal fluid investigations were available. All patients were followed for at least 72 hours until the final diagnosis was made. Meningitis was diagnosed in 21 children (6%). Of these, 11 were admitted immediately to the intensive care unit, the other 10 (3%) were diagnosed after evaluation in the emergency room. The presence of definite nuchal rigidity, petechiae or coma identified 14 of these 21 meningitis cases. The remaining seven children with meningitis but without any of these signs had complex seizure features or a suspicious history (i.e., an illness for at least 3 days, vomiting or drowsiness at home, a physicians visit in the previous 48 hours). In the absence of these features, there were no meningitis cases. A time lapse longer than 6 hours between the seizure and evaluation at the emergency ward indicated an increased meningitis risk. Age, gender, prior antibiotic or anticonvulsant treatment had no relation with meningitis. The results of the decision analysis were as follows: Only if a delay in treatment of meningitis cases substantially increases mortality and morbidity, routine testing leads to an overall favourable result, at the cost of several hundreds of extra lumbar punctures per 1,000 children with seizures and fever but without meningitis. It is concluded that meningitis in infants and children with seizures and fever can be detected by the presence of clinical indicators. Meningitis is highly improbable in a child without these indicators. Routine investigation of cerebrospinal fluid is not cost-effective.

MANAGEMENT OF RECURRENT SEIZURES

The management of recurrent febrile seizures is addressed in *Chapter 4*. Here, the risk of frequent or severe recurrences that, conceivably, might carry some risk of persistent neurological damage is most relevant. First, a study describing the phenonemon of recurrent febrile seizures as a function of time since the first occurrence and certain risk factors is presented (*Section 4.1*). A further evaluation of the role of the child's age and these risk factors is performed in a collaborative study described in *Section 4.2*. Finally, in *Section 4.3* a synthesis of all prevailing information is achieved in the form of a risk model for seizure recurrence. The model's predictions are validated in a separate dataset.

In *Section 4.1* the results of a follow up study among 155 Dutch children who visited the emergency room after experiencing their first febrile seizure are presented. Median follow up time was 38 months (range 27 to 60). Of these 155 initially untreated children 37% suffered at least one, 30% at least two and 17% at least three recurrent febrile seizures. The vulnerable period for recurrent seizures after a first febrile seizure was between the ages of 12 and 24 months, whereafter it was four to five times lower. The recurrence hazard after any seizure was highest in the first six months, and declined steadily after 6 months without seizures. The risk of multiple recurrences was assessed. A first degree family history of febrile or non-febrile seizures was a predictor of multiple

recurrences; an age of at least 30 months and a temperature of 40.0° C or higher at the initial seizure were associated with a decreased risk. Several factors acted together on the risk of recurrent seizures, sometimes in opposite directions. By considering the action of all relevant factors (age at onset, family history and features of the initial febrile seizure) subgroups of children with a one year seizure recurrence rate as low as 15% and as high as 48% were identified.

To reassess the relations between the postulated risk factors and seizure recurrence after a first febrile seizure the individual data from 5 follow-up studies that used similar definitions of febrile seizures and risk factors were pooled and re-analyzed (*Section 4.2*). The risk of frequent recurrent seizures and occurrence of complex seizures in previously healthy, untreated children was studied. Seizure recurrence hazard was described as a function of the child's attained age. The influence of various risk factors on the recurrence hazard was assessed, controlling for other factors. Of a total of 2496 children with 1410 episodes of recurrent seizures, 32% had one, 15% had two and 7% had three or more recurrent seizures after a first febrile seizure. Seven percent had a complex recurrence. The hazard of recurrent seizures was highest between the ages of 12 and 24 months. After a first and a second recurrence, the risk of further febrile seizures was 2 and 2.5 times higher, respectively. A history of febrile or unprovoked seizures in a first degree family member and a relatively low temperature at the first seizure were also associated with an increased risk of subsequent recurrences. 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. A higher recurrence rate in clinic-based studies compared with population-based studies could not be explained by a difference in the presence of the risk factors studied. Thus, other factors must influence seizure recurrence after an initial febrile seizure.

In the study described in *Section 4.3* the risk factors identified in the previous sections were combined into a single prognostic index. From this index the risk of further febrile seizures was calculated at various points in time. Separate attention was given to the risk of a complex recurrence. The validity of the predictions was tested in a separate dataset concerning 347 children with febrile seizures; estimated recurrence risk and observed number of recurrences in various risk strata were compared. The predictive model appeared to be well calibrated. Using all relevant information, predictions with a precision of plus/minus 4% were achieved. The model may be used to counsel parents who seek advice about their child's risk of recurrent febrile seizures and the need for prophylaxis.

GENERAL DISCUSSION AND CONCLUSIONS

Finally, in the General Discussion (*Chapter 5*) the results of all studies and their implications for management are reexamined in the context of a case history of a boy that is seen in the emergency room. It is evident that still many issues surrounding seizures associated with fever in young children are unresolved. The studies described above may have created a picture with more detail, but large areas are still hazy. Therefore, it

is imperative that further appropriately designed clinical studies focus on the uncertainties discussed.

Samenvatting

TWEE TOT VIER PROCENT VAN ALLE KINDEREN MAAKT OOIT EEN CONVULSIE BIJ koorts door. Dit blijkt althans uit onderzoek in de Verenigde Staten en in Engeland, het is tot nog toe niet bekend hoe vaak deze aanvallen optreden bij Nederlandse kinderen.

Tijdens de eerste evaluatie na een aanval moet de arts bepalen of er een onderliggende oorzaak is die directe behandeling behoeft. Een van de belangrijkste vragen daarbij is of er bij alle kinderen een lumbaalpunctie (LP) dient te worden verricht om meningitis uit te sluiten. Overweging is hierbij of men op grond van de bevindingen uit anamnese en lichamelijk onderzoek van een LP kan afzien zónder een meningitis te missen. Gezien het feit dat in de meeste gevallen het ondergaan van een LP voor het kind een traumatische ervaring betekent, zal de arts liefst alleen een LP verrichten indien er een duidelijke verdenking bestaat op meningitis.

Wanneer behalve de koorts geen onderliggende oorzaak voor de convulsie wordt gevonden, spreekt men van een koortsconvulsie. Koortsconvulsies moeten worden onderscheiden van epilepsie. Van epilepsie spreekt men wanneer er meerdere convulsies zonder koorts optreden. In het algemeen is de prognose na een eerste koortsconvulsie goed. Het grootste probleem is het frequent optreden van recidief koortsconvulsies. Hoe vaak en bij welke kinderen zulke recidieven het meest optreden is tot nu toe niet bekend. Het is mogelijk om met anti-epileptica de kans op recidief koortsconvulsies te verlagen. Echter, de hierbij gebruikte medicamenten hebben ongewenste bijwerkingen zoals sufheid, druk gedrag, concentratie stoornissen en maag-darm klachten. De vraag is daarom welke kinderen voor een profylactische behandeling in aanmerking komen, en bij welke kinderen de nadelen (bijwerkingen, medische controle) niet opwegen tegen de voordelen (verlaging recidiefkans).

Ondanks het relatief vaak voorkomen van convulsies bij koorts, is het niet altijd duidelijk welk beleid met betrekking tot diagnostisch onderzoek en medicamenteuze behandeling optimaal is. In dit proefschrift worden de hier boven gestelde vragen nader onderzocht, en wordt getracht antwoorden te formuleren aan de hand van de resultaten van een aantal onderzoeken bij kinderen met convulsies bij koorts. Enkele van deze

onderzoeken werden in Nederland uitgevoerd. Daarnaast werden gegevensbestanden gebruikt van elders uitgevoerd onderzoek.

INTRODUCTIE

In de introductie (*Hoofdstuk 1*) worden de verschillende verschijningsvormen van convulsies bij koorts besproken. Men onderscheidt ongecompliceerde en gecompliceerde convulsies (Engels 'simple' en 'complex'). Een eenmalige gegeneraliseerde aanval korter dan 15 minuten is ongecompliceerd; langdurige, partiële (of focale), en meerdere convulsies binnen 24 uur noemt men gecompliceerd. Het belang van de anamnese en het lichamelijk onderzoek voor het maken van een differentiaal diagnose wordt benadrukt.

EPIDEMIOLOGIE

In *Hoofdstuk 2* worden de onderzoeken met betrekking tot de epidemiologie van convulsies bij koorts in Rotterdam beschreven. Eerst werd onderzoek verricht naar het vóórkomen van deze aanvallen bij schoolkinderen (*Hoofdstuk 2, Paragraaf 2.1*). Tijdens een routine onderzoek bij de schoolarts werd aan de ouders van 3.570 Rotterdamse kinderen van 6 jaar gevraagd of hun kind ooit een convulsie bij koorts had doorgemaakt. In totaal hadden 140 kinderen een dergelijke aanval gehad (3,9%, 95% betrouwbaarheids interval: 3,3% tot 4,5%). Bij 14% waren er meerdere aanvallen tijdens dezelfde koortsperiode geweest, bij 26% waren er nieuwe aanvallen tijdens latere koorts-episoden geweest. De mediane leeftijd bij de eerste aanval was 18 maanden. Een derde had direct na de aanval het ziekenhuis bezocht. In 5,4% van alle 3.570 kinderen was er sprake van een ouder, broertje of zusje met convulsies bij koorts; deze kinderen hadden een 4,5 maal hogere kans op het zelf doormaken van een convulsie bij koorts dan kinderen zonder een eerste graad familielid met dergelijke aanvallen.

Uit deze eerste studie bleek ook dat niet alle kinderen met een convulsie bij koorts op de EHBO in het ziekenhuis worden gezien. In *Paragraaf 2.2* wordt op basis van de resultaten van een enquête-onderzoek onder alle 316 huisartsen in de regio Rotterdam en een onderzoek door het Nederlands Instituut voor onderzoek in de Eerste Lijn (NIVEL) de fractie kinderen met convulsies bij koorts geschat die niet in het ziekenhuis wordt gezien. Uit de resultaten blijkt dat waarschijnlijk 50% van alle convulsies bij koorts door de huisarts thuis wordt behandeld, en dat voornamelijk kinderen met gecompliceerde aanvallen naar het ziekenhuis worden verwezen. Zo blijkt er dus sprake te zijn van een aanzienlijke kwantitatieve en kwalitatieve selectie van kinderen voordat zij op de EHBO van een ziekenhuis worden gezien. Er is echter ook een grote groep kinderen die door hun ouders na een convulsie rechtstreeks naar het ziekenhuis wordt gebracht. De ziektekundige verschillen tussen kinderen die door de huisarts naar de EHBO zijn verwezen en die door de ouders direct naar de EHBO worden gebracht, worden nader beschreven in de *Hoofdstukken 3 en 4*.

HET BELEID OP DE EHBO

In *Hoofdstuk 3* worden de resultaten van het onderzoek naar de diagnostische waarde van anamnese en lichamelijk onderzoek voor het stellen van de diagnose **meningitis** op de EHBO beschreven. Hierbij werd samengewerkt met de afdeling Kindergeneeskunde van het Juliana Kinderziekenhuis in Den Haag en de afdeling Kindergeneeskunde van het Zuiderziekenhuis in Rotterdam. In een eerste onderzoek werd klinische informatie geïdentificeerd die op de EHBO wijst op het bestaan van meningitis (*Paragraaf 3.1*). Bij 309 achtereenvolgende kinderen die zich presenteerden met een convulsie bij koorts op de EHBO van het Sophia Kinderziekenhuis en het Juliana Kinderziekenhuis werd in 23 gevallen een meningitis vastgesteld (7%, 95% betrouwbaarheids interval: 4% tot 10%). Deze 23 kinderen werden vergeleken met 69 'at random' geselecteerde kinderen uit de groep met een convulsie bij koorts maar zónder meningitis. Door de aanwezigheid van *petechiën*, duidelijke of dubieuze *nekstijfheid*, (sub)*coma* en een *parese of paralyse* aan een of meer ledematen konden 21 van de 23 kinderen met meningitis worden geïdentificeerd. De twee kinderen met meningitis maar zónder deze klinische verschijnselen hadden een *gecompliceerde convulsie* doorgemaakt (langdurig en partieel). Bij kinderen met een ongecompliceerde aanval bij wie geen anamnestische alarmsymptomen aanwezig waren (dat wil zeggen: korter dan 3 dagen ziek, géén overgeven of sufheid voor de aanval) kwam geen meningitis voor. Deze resultaten tonen aan dat aan de hand van anamnese en lichamelijk onderzoek meningitis op klinische gronden met grote waarschijnlijkheid kan worden uitgesloten, en dat er dus geen reden is om LP's te verrichten bij alle kinderen met een convulsie bij koorts.

In een prospectief onderzoek (*Paragraaf 3.2*) werden de bevindingen uit deze studie getoetst. Gedurende twee jaar werden alle kinderen die zich in een van de drie ziekenhuizen presenteerden met een convulsie bij koorts nauwkeurig onderzocht, vóórdat werd overgegaan tot nadere laboratorium diagnostiek (waaronder vaak een LP). Bij 365 kinderen werden gegevens vastgelegd over de bevindingen bij lichamelijk onderzoek en de anamnese. Alle kinderen werden gedurende 72 uur vervolgd om de uiteindelijke diagnose vast te stellen: meningitis of géén meningitis. Bij 21 kinderen werd een meningitis gevonden (6%, 95% betrouwbaarheids interval: 3% tot 8%). Echter, 11 van deze kinderen waren zo ziek dat zij door de verwijzend arts direct naar de intensive care afdeling werden ingestuurd. De andere 10 gevallen van meningitis (3%, 95% betrouwbaarheids interval: 1% tot 4%) werden op de EHBO gediagnostiseerd. Op grond van de aanwezigheid van petechiën, nekstijfheid, en of coma konden 14 van alle 21 gevallen direct worden geïdentificeerd. Alle 7 andere kinderen met meningitis hadden een gecompliceerde convulsie doorgemaakt. Leeftijd, geslacht, tevoren gebruik van antibiotica en of diazepam had geen relatie met het bestaan van meningitis. Weer werd bij kinderen met ongecompliceerde aanvallen en zónder bovengenoemde anamnestische alarmsymptomen geen meningitis gezien.

Op grond van deze resultaten werd, met in acht neming van andere relevante factoren—de kans op een fout-positieve en fout-negatieve LP uitslag, de kans op complicaties door de LP procedure, en de kans op een toename in mortaliteit en morbiditeit bij

meningitis, indien deze pas na enkele uren wordt behandeld—berekend onder welke omstandigheden een strategie van routinematig verrichten van LP's bij kinderen met een convulsie bij koorts de beste uitkomsten biedt (zie Tabel 3.2.5 en Tabel 3.2.6). Hierbij werd aangenomen dat kinderen zónder meningitis na een observatie-periode van enkele uren hersteld zijn, en dat kinderen met meningitis klinisch als zodanig herkenbaar zijn; LP en antibiotische behandeling in deze laatste groep volgt dus enkele uren na binnenkomst. Alleen als uitstel van de behandeling van kinderen met meningitis gedurende enkele uren een substantiële toename in mortaliteit en morbiditeit veroorzaakt, leidt het routinematig verrichten van LP's tot een algeheel gunstiger resultaat. Dit gebeurt dan ten koste van circa 450 extra LP's per 1.000 kinderen met een convulsie bij koorts maar zónder meningitis. Echter, als de LP procedure zelf gepaard gaat met morbiditeit en mortaliteit, hoe gering ook, zal een strategie van LP op klinische indicatie (dat wil zeggen bij gecompliceerde aanvallen en bij manifeste klinische verschijnselen van meningitis) altijd het gunstigste resultaat opleveren.

Geconcludeerd wordt dat meningitis bij kinderen met convulsies bij koorts op de EHBO met grote waarschijnlijkheid kan worden uitgesloten aan de hand van anamnese en lichamelijk onderzoek, en dat er geen medische reden is om routinematig LP's te verrichten.

RECIDIEF KOORTSCONVULSIES

Na een eerste aanval moet men rekening houden met de mogelijkheid van recidief koortsconvulsies tijdens nieuwe koorts-episoden. *Hoofdstuk 4* beschrijft het onderzoek met betrekking tot recidief koortsconvulsies en de huidige verwachtingen ten aanzien van medicamenteuze profylaxe.

In *Paragraaf 4.1* worden de resultaten gepresenteerd van een vervolgonderzoek bij 155 tevoren gezonde kinderen, die het Sophia Kinderziekenhuis bezochten in verband met een eerste koortsconvulsie. De kinderen werden niet profylactisch met anti-epileptica behandeld. De mediane follow-up tijd was 38 maanden (spreiding 27–60). Achtenvijftig kinderen (37%) maakten tenminste één, 47 (30%) tenminste twee, en 27 (17%) drie of meer recidieven door. De kans op recidieven was niet constant in de tijd: gedurende de eerste zes maanden na de initiële convulsie was deze 20%, en gedurende het tweede halfjaar 11%. De meeste recidieven traden op tussen de leeftijd van 12 en 24 maanden. Een positieve eerste graad familie anamnese voor epilepsie of koortsconvulsies bleek geassocieerd te zijn met het optreden van meerdere recidief convulsies. Een temperatuur boven de 40° C ten tijde van de eerste koortsconvulsie bleek een relatieve bescherming te geven tegen verdere convulsies. Gecompliceerde eerste aanvallen leidden echter niet vaker tot recidieven. Door gebruik te maken van combinaties van relevante risico-factoren (leeftijd, familie anamnese en kenmerken van de eerste koortsconvulsie) kon een groep kinderen met een kans van 48% op recidief convulsies binnen 12 maanden worden onderscheiden van een groep met een recidiefkans van 15%.

De gevonden risico-factoren (leeftijd, familie anamnese voor koortsconvulsies of epilepsie, temperatuur bij de eerste aanval) werden hierna nader onderzocht door middel van een meta analyse van de individuele patiënt-gegevens uit vier andere follow up studies (*Paragraaf 4.2*). Deze studies gebruikten dezelfde definities en in- en exclusie criteria als de Rotterdamse studie, beschreven in *Paragraaf 4.2.* Nadat in multivariate analyses de relatie van de risico-factoren met het optreden van recidief koortsconvulsies in de afzonderlijke studies was onderzocht, werden de gegevens samengebracht in één dataset. Bij een totaal aantal van 2.496 kinderen werd bij 31% tenminste één, bij 15% tenminste twee, en bij 7% drie of meer recidieven gezien. De meeste recidieven traden op binnen 6 maanden na de eerste aanval en vóór de leeftijd van 2,5 jaar. Gecompliceerde recidieven traden op in 7%, maar recidief aanvallen die langer dan 15 minuten duurden kwamen in slechts 2% voor. Een positieve eerste graad familie anamnese voor koortsconvulsies of epilepsie, en een temperatuur lager dan 40° C bij de eerste aanval waren geassocieerd met een verhoogde recidiefkans. In geval van recidieven was het aantal doorgemaakte koortsconvulsies bepalend voor de kans op verdere aanvallen. Tenslotte werd geconcludeerd dat er, naast de in dit proefschrift onderzochte risico-factoren, andere factoren van invloed moeten zijn op de kans op recidief koortsconvulsies.

Zoals in de studie in *Paragraaf 4.1* en in de andere follow up studies werd gevonden, varieert de kans op herhaalde koortsconvulsies van 15% tot 80%, afhankelijk van de aanwezigheid van risico-factoren. In *Paragraaf 4.3* wordt een voorspellend model gepresenteerd waarmee voor kinderen van verschillende leeftijden en met verschillende risico-factoren de kans op recidief koortsconvulsies kan worden geschat. Voor deze schattingen wordt het materiaal gebruikt uit *Paragraaf 4.2.* De accuratesse van de voorspellingen wordt getoetst in een aparte set gegevens, afkomstig van een recente follow up studie onder 347 kinderen. Het blijkt dat de voorspellingen precies en nauwkeurig zijn (gemiddeld plus of min 4%). Geconcludeerd wordt dat het voorgestelde model bruikbaar is bij de behandeling van kinderen met koortsconvulsies.

DISCUSSIE EN CONCLUSIES

In *Hoofdstuk 5* worden alle bevindingen en hun implicaties voor de kindergeneeskundige behandeling besproken aan de hand van een patiënt die op de EHBO wordt gezien na een eerste convulsie bij koorts. Ook komt de nog ontbrekende kennis over dit syndroom aan de orde, welke nodig is voor een rationele behandeling. De boven beschreven studies hebben weliswaar meer inzicht gegeven in tot op heden onderbelichte aspecten, maar vele vragen zijn nog onbeantwoord. Geconcludeerd wordt dat toekomstig onderzoek in dit veld zich dient te richten op de onzekerheden rond de belangrijkste beslissingen in de behandeling van kinderen met convulsies bij koorts.

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Curriculum vitae

Martin Offringa (1958) attended secondary school in The Hague. After his medical training at the Erasmus University in Rotterdam, he spent 2 years as a resident in Internal Medicine, Paediatrics and Cardiology (1986 and 1987). In 1987 he joined the Rotterdam Center for Clinical Decision Analysis (headed by Prof. Dr J. Lubsen). He received a training in epidemiology and clinical decision analysis, and took courses by K. Rothman and O. Miettinen. Between 1988 and 1990 the data of the work described in this thesis were collected. During this period he participated as a teacher in national and international courses on clinical decision analysis and management of febrile seizures.

From 1990 to 1995 he received his training in paediatrics at the Rotterdam Sophia Children's University Hospital (headed by Prof. Dr H.K.A. Visser), and at the Juliana Children's Hospital in The Hague (headed by Dr A.J. van der Heyden). During this period, the manuscripts for this thesis were finished. At present he is a fellow in Neonatology at the department of Paediatrics, Emma Children's Academic Medical Center in Amsterdam.

Informatiefolder koortsstuipen

Naam arts:

Telefoonnummer:

Uw kind heeft een koortsstuip doorgemaakt. Voor de meeste mensen is het meemaken van een dergelijke aanval een zeer angstwekkende ervaring. Waarschijnlijk heeft u op dit moment dan ook vele vragen over dit soort aanvallen. Via deze folder hopen wij op enkele van deze vragen antwoord te geven. Maar aarzel niet vragen te stellen. De naam van de arts bij wie u terecht kunt, vindt u hierboven. U kunt uiteraard ook uw huisarts raadplegen.

Wat is een koortsstuip?
Een stuip of een convulsie is een plotseling optredende stoornis in de (electrische) functie van de hersenen, welke bewusteloosheid en meestal spiertrekkingen veroorzaakt. Bij jonge kinderen kan bij een koortsende ziekte een dergelijke aanval optreden; we spreken dan van een koortsstuip. Koortsstuipen moeten worden onderscheiden van epilepsie. Van epilepsie spreekt men wanneer er meerdere stuipen zonder koorts optreden.

Koortsstuipen komen regelmatig voor. Circa vier procent van alle kinderen maakt ooit een koortsstuip door. De aanvallen treden alleen op bij kinderen tussen de leeftijd van 6 maanden en 6 jaar. Het is dus typisch een probleem van jonge kinderen.

Tijdens een aanval is het kind bewusteloos, voelt geen pijn en kan soms enkele seconden met ademhalen stoppen. Het zien van deze aanvallen wekt in het algemeen een enorme schrik. Het is echter goed om te weten dat een koortsstuip geen schade aan de hersenen veroorzaakt. Kinderen overlijden nooit tijdens een dergelijke aanval. Na een fase van complete bewusteloosheid—met of zonder spiertrekkingen—komt het kind snel weer bij, maar maakt een uitgeputte indruk. Hierna volgt dan meestal een diepe slaap. Soms is er hoofdpijn na een aanval.

De hoge koorts, waarbij doorgaans de stuipen optreden, kan vele oorzaken hebben. Onderzoek wijst uit dat de koorts bij kinderen met een koortsstuip meestal wordt veroorzaakt door een verkoudheid of een keel- of oorontsteking. Soms zal de arts echter geen oorzaak van de koorts kunnen vinden.

Welke gevolgen heeft een koortsstuip?
Zoals gezegd veroorzaken koortsstuipen geen schade aan de hersenen. Uit onderzoek is gebleken dat verreweg de meeste kinderen zich na een koortsstuip verder geheel normaal ontwikkelen. Wel doet zich bij circa 30% van de kinderen die eenmaal een dergelijke aanval heeft gehad, een herhaling voor. Deze aanvallen zijn gelukkig in het algemeen kort en gaan vanzelf over. Tien procent van de kinderen met koortsstuipen maakt drie of méér aanvallen door. De kans op herhaalde aanvallen verschilt van kind tot kind; hoe precies is niet bekend. De kans dat zich later epilepsie ontwikkelt is erg klein, en hangt samen met het voorkomen van epilepsie in de familie.

Hoe te handelen bij een nieuwe koortsstuip?
Het is dus mogelijk dat bij een nieuwe koortsperiode er opnieuw een koortsstuip optreedt. Enkele adviezen—

1. Blijf kalm.
2. Zorg dat het kind zich niet kan verwonden, leg het op een zachte ondergrond. Draai het op de zij of op de buik met het hoofd opzij, zodat het vrij kan ademen. Indien er voeding of een ander voorwerp in de mond is, probeer dit dan voorzichtig te verwijderen.
3. U kunt de inhoud van een tube Stesolid® in de anus toedienen. Doe dit alleen als de aanval (bewusteloosheid én trekkingen) nog bezig is. Binnen enkele minuten zal de aanval stoppen. Vaak is echter de aanval al voorbij, voordat men de kans heeft gehad de Stesolid toe te dienen. Het is dan niet meer nodig om het te geven.
4. Indien de aanval niet na 5 à 10 minuten stopt, kunt u eventueel een tweede maal Stesolid geven. Als hierna de aanval nog niet stopt, neem dan direkt contact op met de huisarts of ga direkt naar het ziekenhuis. Er kunnen dan medicijnen in de bloedbaan worden toegediend.
5. Na een koortsstuip moet het kind altijd door een arts worden nagekeken. U moet dus contact opnemen met de (dienstdoende) huisarts. Deze zal zoeken naar de oorzaak van de koorts, en eventueel verder onderzoek en/of een behandeling instellen.

Hoe te handelen bij koorts?
Jonge kinderen hebben regelmatig koorts; dit hoort bij deze levensfase. Ook komt op deze leeftijd verkoudheid en een keel- of oorontsteking veel voor. Deze koorts-episoden zijn nauwelijks te voorkomen. Enkele adviezen—

1. Overtuig u ervan dat er werkelijk koorts is en meet de temperatuur.
2. Probeer een indruk te krijgen over de oorzaak van de koorts. Overleg eventueel met de huisarts.
3. Kleed het kind luchtig aan, en laat het onder een dunne deken slapen. Het is niet nodig de koorts te onderdrukken; een nieuwe koortsstuip kan men hiermee niet voorkómen. Indien u tóch een koortswerend middel wilt geven, doe dit dan in overleg met uw huisarts of kinderarts. Bij kinderen die gevoelig zijn voor koortsstuipen is een nauwkeurige dosering en een regelmatige toediening namelijk van groot belang.

Besluit
In het voorgaande hebben wij willen aangeven dat—

1. Koortsstuipen veel voorkomen en, hoewel angstwekkend, zij in principe onschuldig zijn.
2. Koortsstuipen vooral bij jonge kinderen optreden en in het algemeen maar één keer optreden. Bij sommige kinderen komen echter herhaalde aanvallen voor.
3. Koortsstuipen zéér zelden later door epilepsie worden gevolgd.
4. U bij een eventuele herhaalde koortsstuip thuis iets kunt doen. Draai het kind op de de zij of buik, zodat het vrij kan ademen. Zorg dat u altijd Stesolid® in huis hebt. Na een koortsstuip roept u altijd de hulp van een arts in.
5. U een aantal algemene maatregelen kunt nemen bij koorts.

Tenslotte
Verschillende artsen geven verschillende adviezen over de koortsstuipen. Aarzel niet om alle vragen die u rond dit onderwerp heeft met uw arts te bespreken.